TETRAHEDRON LETTERS

The International Organ for the Rapid Publication of Preliminary Communications in Organic Chemistry

1960

HONORARY REGIONAL EDITORS

Prof. W. DOERING: 1901-A Yale Station, New Haven, Connecticut, U.S.A.
Prof. R. H. MARTIN: Laboratoire de Chimie Organique, Université Libre de Bruxelles, 50 Ave. F. D. Roosevelt, Brussels, Belgium.
Prof. A. N. NESMEYANOV: Akademiya Nauk SSSR, Bolshaya Kaluzhskaya 14, Moscow, U.S.S.R.
Prof. F. WEYGAND: Organisch-chemisches Institut, Technische Hochschule, München 2, Germany.

EXECUTIVE EDITOR

Prof. H. STEPHEN: 79 Hurst Rise Road, Cumnor Hill, Oxford, England.

HONORARY EDITORIAL ADVISORY BOARD

Europe

O. ACHMATOWICZ—Warsaw
K. BALENOVIĆ—Zagreb
D. H. R. BARTON—London
ENDRE BERNER—Oslo
A. J. BIRCH—Manchester
J. W. CORNFORTH—London
C. DUFRAISSE—Paris
H. ERDTMAN—Stockholm
G. FODOR—Budapest
C. A. GROB—Basel
E. HAVINGA—Leiden
B. HELFERICH—Bonn
M. JULIA—Paris
P. KARRER—Zurich
G. W. KENNER—Liverpool
E. LEDERER—Paris
R. P. LINSTEAD—London
M. LORA-TAMAYO—Madrid
G. OURISSON—Strasbourg
R. PAUL—Paris
V. PRELOG—Zurich
A. QUILICO—Milano
R. ROBINSON—London (Co-Chairman)
L. RUZICKA—Zurich
F. SORM—Prague
M. STACEY—Birmingham
A. TODD—Cambridge
W. TREIBS—Leipzig
T. URBAŃSKI—Warsaw
S. VEIBEL—Copenhagen
L. VELLUZ—Paris
F. WESSELY—Vienna
T. S. WHEELER—Dublin
O. WICHTERLE—Prague
G. WITTIG—Heidelberg

American Continents

P. D. BARTLETT—Cambridge, Mass.
H. C. BROWN—Lafayette
V. DEULOFEU—Buenos Aires
M. J. S. DEWAR—Chicago
C. DJERASSI—Stanford
W. S. JOHNSON—Madison
L. MARION—Ottawa
J. D. ROBERTS—Pasadena
A. SANDOVAL—Mexico
G. STORK—New York
A. WEISSBERGER—Rochester
K. WIESNER—New Brunswick
S. WINSTEIN—Los Angeles
R. B. WOODWARD—Cambridge, Mass. (Co-Chairman)

The East

E. D. BERGMANN—Tel-Aviv
L. H. BRIGGS—Auckland
D. GINSBURG—Haifa
HUANG-MINLON—Shanghai
T. R. SESHADRI—Delhi
C. W. SHOPPEE—Sydney
F. SONDHEIMER—Rehovoth
S. SUGASAWA—Tokyo
K. TAKEDA—Japan
K. VENKATARAMAN—Poona

Secretary to the Board of Editors: Dr. T. STEPHEN, 79 Hurst Rise Road, Cumnor Hill, Oxford
Sub-editor: I. STUART, Journals Dept., Pergamon Press Ltd., Headington Hill Hall, Oxford

NUMBERS 1–27 1960

Copyright © 1960 Pergamon Press Ltd.

PERGAMON PRESS LTD.

OXFORD LONDON NEW YORK PARIS

NOTES TO CONTRIBUTORS PREPARING PRELIMINARY COMMUNICATIONS AND LETTERS FOR SUBMISSION TO TETRAHEDRON LETTERS

To ensure most speedy publication after acceptance by referees (refereeing is usually done within 24 hours) it is desirable, *but not essential*, for manuscripts to be submitted in a form suitable for direct photographic reproduction. Accepted papers not received in reproducible form will be retyped by the Press and a carbon copy will be sent to the senior author for checking and prompt return. Extensive alterations to the original text are not encouraged and any such alteration will inevitably lead to a delay in publication. Authors preparing manuscripts for direct photographic reproduction should ensure that their typist follows the instructions given below.

Typing Instructions

(1) Manuscripts must be typed (double spaced) on one side of the paper, with a page typing area of about 6¼ inches wide by 9 to 9¼ inches deep.
(2) Please use a good *black* typewriter ribbon (silk ribbon preferred). Do not use *blue* ribbon. (Blue does not come out on photographic reproductions.)
(3) Please clean typewriter keys before starting, so that a good clear impression is obtained.
(4) Please provide clean manuscript pages, devoid of bad erasure marks, smudges, etc.

Hand Lettering

Use *black* ink (never blue) whenever it is necessary to letter mathematical symbols, etc., by hand. Organic formulae should be drawn in black ink, or accurately and lightly indicated in soft blue pencil so that they may be properly drawn in at the publishing office for reproduction. Number each page at the *bottom* of the sheet lightly in blue pencil.

Headings

Title. Set the title in capitals centred on the width of the page. The top of the title should be 1 inch from the top of the typing area. After one line space, type the author's name and address on separate lines in upper and lower case letters (i.e. *not* all in capitals).
Major headings should be underlined and centred on the page width.
Sub-headings should be underlined and placed flush on the left-hand margin of the column on a separate line.
Sub-sub-headings should be underlined, indented and run in at the beginning of the paragraph.

References as for *Tetrahedron*

All bibliographical references should be listed as footnotes and should be set out as described in the "Notes to Contributors" to be found in every copy of *Tetrahedron*, (i.e. as footnotes to the page on which they are first mentioned). When referring to them in the text, type the corresponding reference number in superscript form as shown at the end of this sentence.[2]

Equation Numbers in Parentheses

When numbering equations, enclose numbers in parentheses and place flush with right-hand margin of the column.

Symbols and Abbreviations

Use only standard symbols and abbreviations in text and illustrations.

Reprints

A reprint order form together with notification of acceptance will be sent. Please return this form promptly to ensure that your reprints are sent to you after publication of the issue, and to avoid incurring additional charges in their reproduction.

ILLUSTRATIONS

Drawings and Photographs

(1) Original drawings of all diagrams and glossy prints of all photographs must be supplied in order to ensure good clear reproduction. Please leave adequate room in the typescript for illustrations to be inserted, and please type in captions at the appropriate place, taking care to avoid confusion with the test.

(2) All lines on diagrams should be black on white paper and heavy enough to remain legible after reduction. *Do not use* a fine screen graph paper.

(3) All lettering should be large enough to remain legible after reduction.

(4) Please omit all unessential illustrations.

(5) The author's name and the figure number should be indicated lightly in pencil on the back of each illustration.

Mailing of Manuscripts

Please send your manuscripts by airmail, securely packed, to:

"Tetrahedron Letters"
Pergamon Press

122 East 55th Street
New York 22, N.Y.

OR

Headington Hill Hall
Oxford

whichever address is more convenient.

PRINTED IN NORTHERN IRELAND AT THE UNIVERSITIES PRESS, BELFAST

1960

LIST OF CONTENTS

NUMBER 1

A. N. NESMEYANOV, E. G. PEREVALOVA and T. V. NIKITINA: Azoferrocene 1
M. LÖW: The conformation of cyclopentane 3
V. BRUCKNER, A. KARCZAG (WILHELMS), K. KÖRMENDY, M. MESZAROS and J. TOMASZ: Einfache Synthese des Pentacens 5
K. G. VAN SENDEN and C. KONIGSBERGER: Hydrolysis of benzylidene aniline in the presence of cetyl trimethyl ammoniumbromide 7
J. SMITH and R. H. THOMSON: Spinochrome E 10
H. C. VAN DER PLAS and H. J. DEN HERTOG: Synthesis of the isomeric sulphonic acids of 2,6-di-tert.-butylpyridine 13
MIGUEL A. ONDETTI and VENANCIO DEULOFEU: Alkaloids from *Aspidosperma australe* Müll. Argov. (Note II). The structure of olivacine and *u*-alkaloid C (guatambuine) 18
G. W. KENNER, R. C. SHEPPARD and C. E. STEHR: Synthesis of thiazole amino-acids derived from natural peptides 23

NUMBER 2

C. N. R. RAO, J. RAMACHANDRAN and G. K. GOLDMAN: Substituent and solvent effects on the n → π^* ($^1U \leftarrow {}^1A$) transition in aliphatic carbonyl derivatives: evidence for hyperconjugation in the excited states of molecules 1
S.-O. LAWESSON and C. BERGLUND: Studies of peroxycompounds. Copper salt catalyzed reactions of t-butyl perbenzoate with benzyl ethers 4
A. T. BALABAN and C. D. NENITZESCU: Preparation of pyrylium salts by olefin diacylation. The two pyrylium salts formed in amylene diacetylation with various catalysts 7
A. G. ANDERSON, JR. and W. F. HARRISON: Electrophilic substitution in cyclopenta [c] thiapyran 11
L. ÖTVÖS, J. MÁRTON and J. MEISEL-ÁGOSTON: Investigation of the reaction between isocyanates and acid anhydrides with ^{14}C 15
L. ÖTVÖS and L. NOSZKÓ: Investigation of the pyrolytic decarboxylation of carboxylic acids with ^{14}C. Mechanism of the formation of camphor from homocamphoric acid 19
J. ELLIS, A. H. JACKSON, G. W. KENNER and J. LEE: Porphyrin nuclear magnetic resonance spectra 23
R. STEWART and R. VAN DER LINDEN: The deuterium isotope effect in the permanganate oxidation of aromatic trifluoromethyl alcohols 28
S. WINSTEIN and JOHN S. GALL: Racemization and radio-chloride exchange of *p*-chlorobenzhydryl chloride in acetone 31

NUMBER 3

KEN'ICHI TAKEDA and KANAME HAMAMOTO: The structure of metagenin 1
J. KREPINSKY, V. HEROUT and F. SORM: The identity of jatamansone and valeranone . . . 9
G. W. GRIFFIN, J. E. BASINSKI and A. F. VELLTURO: Photodimerization of maleic and fumaric acid derivatives 13
K. WIESNER, H. W. BREWER, D. L. SIMMONS, D. R. BABIN, F. BICKELHAUPT, J. KALLOS and T. BOGRI: The structure of neoline 17
A. N. NESMEYANOV, A. E. BORISOV, A. I. KOVREDOV and E. I. GOLUBEVA: Reactions of free radicals and unsymmetrical organo-mercuric compounds 25

NUMBER 4

T. BRUUN: Siphulin, a chromanone type lichen acid 1
H. J. BESTMANN und H. SCHULZ: C-Alkylierung von Triphenylphosphin-carbomethoxy-methylen. Ein neuer Weg zur Synthese von Carbonsäuren 5
H. J. BESTMANN: C-Acylierung von Triphenylphosphin-alkylenen. Ein neuer Weg zu Ketonen 7
N. C. YANG and DING-DJUNG H. YANG: Photochemical reactions of 20-ketosteroids . . . 10
G. I. FRAY, R. H. JAEGER and Sir ROBERT ROBINSON: Synthesis of royal jelly acid . . . 15
F. MONTANARI: The stereochemistry of nucleophilic addition of thiophenols to propiolic acid and ethyl propiolate 18

NUMBER 5

WILLIAM S. JOHNSON, M. NEEMAN and S. P. BIRKELAND: A new reaction of diazomethane with α, β-unsaturated ketones 1
W. BAKER, D. F. DOWNING, A. J. FLOYD, B. GILBERT, W. D. OLLIS and R. C. RUSSELL: Synthesis of irigenin and of tectorigenin, derivatives of 5,7-dihydroxy-6-methoxyisoflavone . . . 6
LEONARD SPIALTER, RUSSELL S. TOWERS and MILLARD M. KENT: Novel synthesis of organo-tri- and di-fluorosilanes with aqueous hydrofluoric acid 11

1960

D. S. Bapat, B. C. Subba Rao, M. K. Unni and K. Venkataraman: The action of diborane and of sodium borohydride–boron trifluoride–etherate on anthraquinones: a new synthesis of aloe-emodin and citreorosein and a general method for the reduction of anthraquinones to anthracene derivatives 15
D. K. Banerjee and K. M. Sivanandaiah: On the stereoselective synthesis of estrone . 20
B. C. Fielding, E. J. Haws, J. S. E. Holker, A. D. G. Powell, A. Robertson, D. N. Stanway and W. B. Whalley: Monascorubrin 24

NUMBER 6

Harold Conroy, Raymond Bernasconi, Peter R. Brook, Raphael Ikan, Roberta Kurtz and Keith W. Robinson: The structure of echitamine 1
R. Bognar and W. Wieniawski: Nitrogen glycosides. N-Glycosyl derivatives of substituted rhodanines 10
L. S. Bartell: Secondary isotope effects and mass-sensitive amplitudes of vibration . . . 13
Bruce R. Penfold and William N. Lipscomb: The structure of HCN tetramer 17
K. Balenovic, N. Bregant and D. Francetic: Oxidation of organic sulphides with optically active peroxy acids. Asymmetric synthesis of sulphoxides 20
Andrew Streitwieser, Jr.: An LCAO treatment of the acidity of hydrocarbons 23
V. N. Gogte, V. S. Palkar and B. D. Tilak: Synthesis of condensed thiophenes, diaryls and dialkyls through aryllithium and alkyllithium derivatives 30

NUMBER 7

A. J. Birch, B. J. McLoughlin and Herchel Smith: The biosynthesis of the ergot alkaloids 1
K. Schlögl und H. Seiler: Ein zweifach überbrücktes Ferrocen 4
J. Krepinsky, M. Romanuk, V. Herout and F. Sorm: Constitution of valeranone 9
H. Budzikiewicz: Bemerkungen zu der Arbeit von S. M. Bloom: "An acid stable cyclohexadienon" 12
F. Smith and A. M. Stephen: Diborane reduction of carboxyl groups in carbohydrates . 17
W. T. Eeles: An X-ray study of the configuration of cevine 24
R. W. Murray: The reaction of dichlorocarbene with anthracene 27
M. C. Perezamador and J. Herran: Turbicoryn, a new glucoside obtained from the seeds of a sacred plant 30
Harry H. Wasserman and Harry R. Nettleton: Indole ring formation from β, β-diphenyleneazobenzene 33

NUMBER 8

T. Kubota, T. Kamikawa, T. Tokoroyama and T. Matsuura: On the chemical constitution of obacunone 1
William S. Johnson and Kenneth V. Yorka: dl-18-Nortestosterone 11
E. E. van Tamelen, G. Brieger and K. G. Untch: Synthesis of a borepin 14
Ernest E. Eliel: The absolute configuration of (+)-3-methyl-t-butyl-1-chloroallene . . 16
E. D. Bergmann and S. Cohen: Organic fluorine compounds. Fluorine derivatives of mevalolactone 20
A. N. Nesmeyanov, A. E. Borisov and N. V. Novikova: Geometrical isomers of stibinous and stibinic propenyl compounds 23
H. Brockmann, H. Brockmann, Jr., J. J. Gordon, W. Keller-Schlierlein, W. Lenk, W. D. Ollis, V. Prelog and I. O. Sutherland: Über die identität von Rutilantinon mit Pyrromycinon und über die Lage der Carbomethoxy-Gruppe in Pyrromycinonen 25
J. J. Gordon, L. M. Jackmann, W. D. Ollis and I. O. Sutherland: Aklavinone . . 28

NUMBER 9

G. H. de Haas and L. L. M. van Deenen: Synthesis of a "mixed-acid" α-lecithin . . 1
H. M. Buck, W. Bloemhoff and L. J. Oosterhoff: The system Lewis acid–nitro compound as a strong electron acceptor 5
G. E. Lewis: Photocatalysed-cyclisation of azobenzene 12
D. Burn, V. Petrow and G. O. Weston: A new reagent for the selective oxidation of steroidal allylic alcohols to $\alpha\beta$-unsaturated ketones 14
M. Fetizon et J. Delobelle: La synthèse totale de l'éther méthylique du nimbiol [(±) méthoxy-6 méthyl-7 podocarpatriène-5,7,13(14)] 16
Roy H. Bible, Jr.: The conversion of podocarpic-acid to nimbiol 20
S. Winstein, Lydia G. Savedoff, S. Smith, I. D. R. Stevens and John S. Gall: Ion pairs, nucleophilicity and salt effects in bimolecular nucleophilic substitution 24

NUMBER 10

F. W. Bachelor, R. F. C. Brown and G. Büchi: The constitution of ring A in aconitine . . 1
D. Chakravarti, R. N. Chakravarti, R. Ghose and Sir Robert Robinson: Echitamine . 10
W. A. Ayer and G. G. Iverach: The structures of α- and β-obscurine 19

Z. VALENTA, H. YOSHIMURA, E. F. ROGERS, M. TERNBAH and K. WIESNER: The structure of selagine 26
HAROLD CONROY: Biogeneis of *Lycopodium* alkaloids 34
GERHARD L. CLOSS and LISELOTTE E. CLOSS: Addition of chlorocarbene to benzene . . 38

NUMBER 11

HEINRICH HAUPTMANN und AURORA CATHARINA GIORA: Acetessigsäure-dithioketale . . 1
P. YATES and P. EATON: Isomerizations in the dicyclopentadiene series 5
G. OHLOFF: Zur thermischen Isomerisation von Citral 10
HANS PLIENINGER und WOLFGANG MÜLLER: Indolopyrone und Pyridone 15
L. DOLEJS, A. MIRONOV and F. SORM: Structure of bulnesol. Stereochemistry of guaiol, nepetalinic acids and iridomyrmecins 18
M. GOUTERMAN and G. WAGNIÈRE: Bond alternation in cycloöctadecanonaene (CON) . . 22
D. CHAKRAVARTI, R. N. CHAKRAVARTI, R. GHOSE and Sir ROBERT ROBINSON: The structure of echitamine (Addendum) 25
A. ILICETO, A. FAVA and U. MAZZUCATO: Thiocyanates and isothiocyanates. Equilibrium kinetics and mechanisms of isomerization 27

NUMBER 12

ROLF HUISGEN, RUDOLF FLEISCHMANN und ALBRECHT ECKELL: Azomethin-imine, eine neue Klasse zwitterionischer Verbindungen 1
ROLF HUISGEN und ALBRECHT ECKELL: 1.3-Dipolare Additionen der Azomethinimine . . 5
RUDOLF GRASHEY, ROLF HUISGEN und HERTA LEITERMANN: 1.3-Dipolare Additionen der Nitrone 9
H. YOSHIMURA, Z. VALENTA and K. WIESNER: A rigorous proof of the selagine structure . . 14
A. FAVA and A. ILICETO: Direct nucleophilic substitution in homologous series. Transmission of polar effects along a hydrocarbon chain 18
D. K. BANERJEE, VINCENT PAUL and S. K. BALASUBRAMANIAN: The total synthesis of 8-isotestosterone 23
WILLIAM S. JOHNSON and RUSSELL A. BELL: A biogenetically patterned concept for the laboratory synthesis of cyclic compounds 27
Errata:
D. CHAKRAVARTI, R. N. CHAKRAVARTI, R. GHOSE and Sir ROBERT ROBINSON: Echitamine . 33

NUMBER 13

D. S. TRIFAN and R. BACSKAI: The role of iron in carbonium ion reactions of ferrocene derivatives 1
LEON M. STOCK and ALBERT HIMOE: Solvent effects on the isomer distribution in the chlorination of aromatics 9
FRANK DOBINSON and PHILIP S. BAILEY: Effect of solvents upon the initial ozone attack on polycyclic aromatics 14
E. A. CHANDROSS and G. SMOLINSKY: The rearrangement of 1-azido-1,2,3-triphenylcyclopropene to 4,5,6-triphenyl-*v*-triazine 19
COLLIN SCHROEDER, SEYMOUR PREIS and KARL PAUL LINK: The mechanism of warfarin formation from 4-hydroxycoumarin and β-anilinobenzylacetone. Evidence for Schiff base intermediates showing enhanced reactivity in the Michael reaction 23
EUGEN MÜLLER, MARTIN BAUER und WOLFGANG RUNDEL: Katalysierte Homologisierung cycloaliphatischer Ketone mit Diazomethan 30
G. I. FRAY, E. D. MORGAN and Sir ROBERT ROBINSON: Synthesis of *cis*-10-hydroxydec-2-enoic acid 34

NUMBER 14

D. BARNARD, G. P. MCSWEENEY and J. F. SMITH: The reaction of ozone with organic hydroperoxides 1
A. MONDON und K. F. HANSEN: Zur Stereochemie der Erythrinane 5
M. ZAORAL and Z. ARNOLD: A novel peptide synthesis 9
A. MELERA, M. GUT and C. R. NOLLER: Structure of cucurbitacin B 13
UMBERTO GIANNINI and SEBASTIANO CESCA: Cyclopentadienyltrimethyltitanium 19
M. HUDLICKÝ: The synthesis of γ-fluoroglutamic acid 21
M. BALASUBRAMANIAN and (Miss) N. PADMA: Conformation of some 4-hydroxy-piperidines . 23

NUMBER 15

ROBERT A. BENKESER, THOMAS V. LISTON and GARTH M. STANTON: Substituent effects in aromatic substitution 1
M. DE MOURA CAMPOS, N. PETRAGNANI and C. THOME: The reaction of diaryl tellurides with vic-dibromides. A new agent of debromination 5

K. BIEMANN: Application of mass spectrometry to structure problems. The carbon skeleton of sarpagine 9
C. R. NOLLER, A. MELERA and M. GUT: Concerning ring A of cucurbitacin B . . . 15
B. E. CROSS, R. H. B. GALT and J. R. HANSON: Gibberellin A_7. A new fungal gibberellin . 18
K. WIESNER, D. L. SIMMONS and R. H. WIGHTMAN: The configuration of delphinine . . 23
D. R. BABIN, J. A. FINDLAY, T. P. FORREST, F. FRIED, M. GOTZ, Z. VALENTA and K. WIESNER: A contribution to the skeletal structure of ryanodine 31

NUMBER 16

ROBERT A. BENKESER, RAM K. AGNIHOTRI and MERWYN L. BURROUS: Reduction of organic compounds by lithium in low molecular weight amines. Highly selective lithium–amine reducing systems 1
K. AGHORAMURTHY, K. G. SARMA and T. R. SESHADRI: The structure of thelephoric acid . 4
K. WIESNER and D. E. ORR: The structure of pithecolobine 11
JEROME A. BERSON: Apportionments of products from unsymmetrically substituted mesomeric carbonium ions 17
H. J. MANNHARDT, F. v. WERDER, K. H. BORK, H. METZ und K. BRÜCKNER: Darstellung von 16-Methylen-steroiden der Corticoid- und Progesteronreihe 21

NUMBER 17

R. F. CHURCH, R. E. IRELAND and J. A. MARSHALL: The stereospecific total synthesis of dl-8β-carbomethoxy-13-oxopodocarpane, a degradation product of phyllocladene . . . 1
W. TREIBS und R. PESTER: Butin-(2)-diol-(1.4)-polymethlyenäther 5
L. H. BRIGGS, B. F. CAIN and B. R. DAVIS: A novel Prévost reaction 9
P. COSSEE: On the reaction mechanism of the ethylene polymerization withheter ogeneous Ziegler–Natta catalysts 12
P. COSSEE: The formation of isotactic polypropylene under the influence of Ziegler–Natta catalysts 17
PETER YATES and DONALD G. FARNUM: Heterocycle formation in the reaction of α-diazoacetophenone with bases 22
W. NAGATA, T. TERASAWA, S. HIRAI und K. TAKEDA: Totalsynthetische untersuchungen der Steroide. Totalsynthese des rac. Pregnan- und Androstanderivatives 27
K. SYHORA: A novel type of the ring opening of the steroidal 16α, 17α-epoxides . . . 34
Erratum:
H. BUDZIKIEWICZ: Bemerkungen zu der Arbeit von S. M. Bloom: "An acid stable cyclohexadienon" 39

NUMBER 18

WILLIAM H. SAUNDERS, JR., SUSAN R. FAHRENHOLTZ and JOHN P. LOWE: The effect of the leaving group on orientation in E2 elimination reactions 1
J. F. BIELLMANN, D. FRANCETIC et G. OURISSON: Effets conformationnels sur l'equilibre *cis–trans* d'α-hydrindanones 4
E. PRICE and N. N. LICHTIN: Ionization and dissociation equilibria of some triphenylchloromethane derivatives in nitrobenzene at 25° 10
N. GETOFF, G. SCHOLES and J. WEISS: Reduction of carbon dioxide in aqueous solutions under the influence of radiation 17
RICHARD B. TURNER and PETER E. SHAW: The total synthesis of a degradation product of phyllocladene 24
MAX FRANKEL, Y. KNOBLER and G. ZVILICHOWSKY: Aminooxy-peptide derivatives of DL-canaline 28
A. MODIANO and M. CAIS: The synthesis of two dihydropentalenyl derivatives 31
PIERRE POTIER, JEAN LE MEN, MAURICE-MARIE JANOT and PETER BLADON: The isolation of spermidine by degradation of lunarine 36

NUMBER 19

LEO MARION, M. WIEWIOROWSKI and M. D. BRATEK: The structure of angustifoline . . 1
O. A. REUTOV, T. P. KARPOV, E. V. UGLOVA and V. A. MALYANOV: The mechanism of isotope exchange reactions of dialkylmercury and alkylmercuric halides 6
HIROSHI SUGINOME: Oxygen heterocycles. The structure of the isoflavanone sophorol . . 16
B. M. CRAVEN: The molecular structure and absolute configuration of picrotoxinin . . 21
L. MANDELL, A. L. NUSSBAUM and E. P. OLIVETO: The structure of neoruscogenin . . 25
E. E. VAN TAMELEN, L. J. DOLBY and R. G. LAWTON: A biogenetically-patterned laboratory in the strychnine–curare alkaloid series 30
A. J. BIRCH, H. F. HODSON, B. MOORE, H. POTTS and G. F. SMITH: Echitamine . . 36

NUMBER 20

K. WEINGES: Die Lignane des Überwallungsharzes der Fichte 1
K. FREUDENBERG und G. S. SIDHU: Die absolute Konfiguration des Sesamins und Pinoresinols 3
F. LINGENS und R. HANKWITZ: Synthese von Acetamido-methylenbernsteinsäure . . . 7
F. A. L. ANET and M. V. RAO: The structure of lycodine 9
F. A. L. ANET: Structure, stereochemistry and interrelation of some *Lycopodium* alkaloids . . 13
P. F. SOMMER, V. P. ARYA und W. SIMON: Über scheinbare Dissoziationskonstanten von Carbonsäuren mit aquatorialer und axialer Lage der Carboxylgruppe 18
LORAND FARKAS und JOZSEF VARADY: Direkt-synthese des Irigenins 23
Z. VALENTA, A. H. GRAY, S. PAPADOPOULAS and C. PODESVA: The structure of quassin . . 25
A. BOWERS, E. DENOT and R. URQUIZA: *Cis* addition of fluorine to a steroid olefin. A new route to 6α-fluoro-Δ^4-3-ketones 34

1960

NUMBER 21

GÜNTHER O. SCHENCK und REINHARD STEINMETZ: Neuratige durch Benzophenon photosensibilisierte Additionen von Maleinsäureanhydrid an Benzol und andere Aromaten . . 1
J. C. BRAUN and G. S. FISHER: Hydroboration of β-pinene 9
R. L. HINMAN and J. LANG: The position of protonation and basicities of indoles . . 12
G. OURISSON et A. RASSAT: Reduction du camphre par les métaux dissous. Obtention sélective d'isobornéol 16
Z. N. PARNES, M. E. VOLPIN and D. N. KURSANOV: New types of hydride transfer . . 20
SHELDON CREMER and R. SRINIVASAN: A photochemical synthesis of bicyclo [2. 2. 0]-hexane 24

NUMBER 22

A. ROMEIKE and G. FODOR: The biogenesis of hyoscine in *Datura stramonium L.* 1
ALMUTH KLEMER: Die Hydrolysengeschwindigkeit der Glykosidischen Bindungen in 4α,6β-Bis-D-glucoside-D-glucose 5
G. H. DE HAAS and L. L. M. VAN DEENEN: Partial synthesis of "mixed-acid" L-α-lecithins . 7
S. WINSTEIN, MASARU HOJO and S. SMITH: Ion pairs, racemization, chloride exchange and the mass law effect in solvolysis of *p*-chlorobenzhydryl chloride 12
DIETMAR SEYFERTH, TADASHI WADA and GUNTER RAAB: The reaction of organolithium reagents with perfluorovinyl derivatives of tin and silicon 20
DAVID LAVIE, YOUVAL SHVO and OTTO RICHARD GOTTLIEB: The stereochemistry of the cucurbitacins 23
R. C. COOKSON, J. HUDEC and R. O. WILLIAMS: Rearrangements of oxo–dicyclopentadienes . 29
KEN'ICHI TAKEDA and HITOSHI MINATO: Absolute configuration of guaiol 33
FRANZ SONDHEIMER, RAPHAEL MECHOULAM and MILON SPRECHER: 19-Hydroxy-10-isotestosterone 38

NUMBER 23

MOHESWAR SHARMA: Synthesis of two stereo-isomers of dehydroabietic acid 1
H. GILMAN, D. J. PETERSON, A. W. JARVIE and H. J. S. WINKLER: The formation of dodecaphenylcyclohexasilane from the reaction of dichlordiphenylsilane with sodium and with lithium . 5
S. S. CHISSICK, M. J. S. DEWAR and P. M. MAITLIS: New heteroaromatic compounds containing two boron atoms 8
R. PETTIT: Synthesis of the thiapyrilium cation 11
TETSUO NOZOE and HITOSHI TAKESHITA: Cuparene and cuprenene 14
RAYMOND C. PETERSON and SIDNEY D. ROSS: Thermal decomposition of 1-azo-bis-1-phenylethane: acceleration by chloranil 18
B. E. CROSS, R. H. B. GALT and J. R. HANSON: Gibberellin A_9 22
C. A. GROB und F. A. JENNY: Mechanistische Uebergaenge bei der Solvolyse von γ-Aminopropylchloriden 25
ENRICO BACIOCCHI, GABRIELLO ILLUMINATI and GIANCARLO SLEITER: Reaction selectivity, hydrogen isotope effect and steric hindrance in the aromatic halogenation of polyalkylbenzenes 30
J. FRIDRICHSONS, A. MCL. MATHIESON and D. J. SUTOR: The molecular structure and absolute configuration of jacobine bromhydrin 35
Errata:
1. K. AGHORAMURTHY, K. G. SARMA and T. R. SESHADRI: The structure of thelephoric acid 38
2. JEROME A. BERSON: Apportionments of products from unsymmetrically substituted carbonium ions 38
3. J. F. BIELLMANN, D. FRACETIC et G. OURISSON: Effets conformationnels sur l'équilibre *cis–trans* d'α-hydrindanones 39

V

NUMBER 24

R. G. BURNS and B. D. ENGLAND: An interpretation of the kinetics of bimolecular substitution by anionic bases in alcohol–water mixtures 1
L. CANONICA, F. PELIZZONI, P. MANITTO and G. JOMMI: Structure of gentiopicroside . . 7
A. T. BLOMQUIST, YVONNE C. MEINWALD, CHARLES G. BOTTOMLEY and PETER W. MARTIN: Dimerization in Finkelstein cyclizations 13
L. H. BRIGGS, B. F. CAIN, R. C. CAMBIE and B. R. DAVIS: Revised structures for mirene and kaurene 18
S. MORRIS KUPCHAN, PETER SLADE and RONALD J. YOUNG: Intramolecular catalysis. Facilitation of alkaline hydrolysis of alicyclic 1,2-diol monoesters 22
GERHARD L. CLOSS and LISELOTTE E. CLOSS: Phenylcarbene from benzylchloride and N-butyllithium 26
T. G. TRAYLOR and P. D. BARTLETT: O^{18} tracer evidence of the termination mechanism in the autoxidation of cumene 30

NUMBER 25

EDWARD C. TAYLOR and W. W. PAUDLER: Photodimerization of some α,β-unsaturated lactams 1
S. WINSTEIN and ROBERT L. HANSEN: An octahydrodimethanonaphthyl non-classical homocyclopropenyl cation 4
LEO J. FILAR and S. WINSTEIN: Preparation and behavior of simple quinone methides . . 9
D. J. BROWN and N. W. JACOBSEN: The unique transannular methylation of 2-amino-4-hydroxypteridine 17
V. BALIAH and M. UMA: Steric enhancement of resonance 21
A. J. BIRCH, D. W. CAMERSON, P. W. HOLLOWAY and R. W. RICKARDS: Further examples and biological C-methylation: novobiocin and actinomycin 26
H. REINBOTHE and K. MOTHES: Ureide biosynthesis in higher plants 32
ROBERT E. IRELAND and PETER W. SCHIESS: The synthesis of dl-sandaracopimaradiene, dl-pimaradiene and some observations on the structure of rimuene 37
NELSON J. LEONARD and MICHAEL J. MARTELL, JR. Laboratory realization of the Schöpf–Oechler scheme in vasicine synthesis 44

NUMBER 26

V. BOEKELHEIDE, O. CEDER, T. CRABB, Y. KAWAZOE and R. N. KNOWLES: The structure of dihydrotoxiferine 1
G. BÜCHI and R. E. MANNING: Structure of verbenalin 5
GIANCARLO BERTI, ANTONIO DA SETTIMO and DOMENICO SEGNINI: The structure of skatole dimer. New reactions of indoline derivatives 13
J. FRIDRICHSONS and A. MCL. MATHIESON: The molecular structure and absolute configuration of thelepogine methiodide 18
HP. FISCHER und C. A. GROB: Synchrone *Cis*-eliminierung bei der Fragmentierung von syn α-Amino-acetophenon-oximen 22
FRANZ SONDHEIMER, YEHIEL GAONI and JUDITH BREGMAN: Acetylenic oxygen heterocycles . 25
ERLING BERNATEK and TORE LEDAAL: Solvolysis of ozonides 30
H. P. FRITZ, J. F. W. MCOMIE and N. SHEPPARD: The infra-red spectrum of $[C_4H_4.Ag]NO_3$. 35
R. BRESLOW, R. BOIKESS and M. BATTISTE: Some cyclopropene rearrangements 42

NUMBER 27

E. C. KIRBY and D. H. REID: Hydride hyperconjugation in 1(3)-methylazulenes 1
K. SCHREIBER und G. ADAM: Synthese von Solanum-alkaloiden aus 3β-Acetoxy-5α-pregn-16-en-20-on 5
K. SCHREIBER und H. RIPPERGER: Absolute Konfiguration des Steroidalkaloids Solanocapsin an C-25 9
L. RAMACHANDRA ROW and G. S. R. SUBBA RAO: A new triterpene carboxylic acid from *Terminalia tomentosa* Wight *et* Arn. 12
MORTIMER J. KAMLET and DONALD J. GLOVER: Substituent effects in the charge–resonance spectra of 1,1-dinitroalkane anions 17
A. R. BATTERSBY and B. J. T. HARPER: Rate study on the incorporation of tyrosine into morphine, codeine and thebaine 21
A. L. ALLRED and C. R. MCCOY: Rapid intermolecular exchange of methyl groups . . 25
M. V. R. KOTESWARA RAO, G. S. KRISHNA RAO and SUKH DEV: Syntheses in the cadinane series: synthesis of (±)-cadinene dihydrochloride 27
G. VOLPP and CH. TAMM: 1α,11α-Epoxy-steroids from ouabagenin by transannular substitution 31

1960

1960

SUBJECT, AUTHOR AND TITLE INDEX TO TETRAHEDRON, VOLUMES 8 TO 11, AND TETRAHEDRON LETTERS,* NUMBERS 1 TO 27

1960

*Reference to *Tetrahedron Letters* is indicated by the letter L prefixing the issue number.

SUBJECT INDEX

Acetamidomethylenesuccinic acid, synthesis, **L20,** 7
Acetic acid, dissociation const. in H_2O–D_2O mixtures, **10,** 207
Acetoacetic acid, dithioketals, prep., **L11,** 1
Acetylaminoalkylthioamides, reaction with ethyl brompyruvate, **L1,** 23
Acetylenic acids, reactions in strong alkali, **8,** 239
Acid anhydrides and isocyanates, reaction study with ^{14}C, **L2,** 15
Acidity, hydrocarbon, LCAO treatment **L6,** 23
Acidolysis of ozonides, formation of peracids, **L26,** 34
Acids, behaviour in H_2O–D_2O mixtures, **10,** 200
carboxylic, pyrolytic decarboxylation study with ^{14}C, **L2,** 19
synthesis, C-alkylation of triphenylphosphine -carbomethoxymethylen, **L4,** 5
cyclohexane carboxylic with axial and equatorial carboxyl groups, apparent p*K* values, **L20,** 18
fatty, reactions in strong alkali, **8,** 221, 239, 246
unsaturated dihydroxy, reactions in strong alkali, **9,** 246
keto- and hydroxy-, fission in strong alkali, **8,** 246
$\alpha\beta$-unsaturated, synthesis from, of iridolactone analogues, **9,** 295
Aconitine, ring A constitution, **L10,** 1
Actinomycin, biosynthesis, C-methylation example, **L25,** 26
Acylation, of 5-aryltetrazoles, **11,** 241
of γ-lysolecithins to "mixed acid" lecithins **L22,** 7
Addition reactions, 1.3-dipolar, to azomethinimine, **L12,** 5
to nitrones, **L12,** 9
Agroclavine, biosynthesis, **L7,** 1
Alantolactone, configuration, **8,** 187
Alcohols, allylic steroidal, oxidation to $\alpha\beta$-unsaturated ketones, **L9,** 14
nimbosterol structure, **10,** 45
primary, catalytic oxidation to aldehydes or carboxylic acids, **9,** 67
reactions in strong alkali, **8,** 246
secondary, catalytic oxidation to ketones, **9,** 67
sesquiterpene, **8,** 42
Aldehydes, heterocyclic, condensation with indole trimethincyanines, **9,** 106
prep., by formulation of condensed aromatic hydrocarbons, **8,** 7
long chain, **9,** 67
Alginic acid propionate, reduction, **L7,** 22
Alicyclic compds., conformational analysis, **9,** 40
molecular geometry and energy considerations, **9,** 40
Alicyclic-1,2-diol esters, alkaline hydrolysis, **L24,** 22
Alkali hydroxides, organic reactions in, **8,** 221, 239, 246
Alkaloids, aconitine, ring A constitution, **L10,** 1
angustifoline structure, **L19,** 1
Aspidosperma australe, **L1,** 18
calycanine synthesis, **8,** 291
delphinine, configuration, **L15,** 23
structure, **9,** 254
dihydrotoxiferine structure, **L26,** 1
echitamine, constitution, **L10,** 10
criticism of proposed structures, **L19,** 36
structure, **L6,** 1; **L11,** 25
ergot, biosynthesis, **L7,** 1
erythrinan, stereochemistry, **L14,** 5
gelsemine degradation, **11,** 148
hydroxylycoctonine, chemistry and structure, **9,** 284
hyoscine biogenesis in *Datura stramonium*, **L22,** 1
lycodine structure, relationship to β-obscurine, **L20,** 9
lycopodium biogenesis, **L10,** 34
structure, stereochemistry and interrelationship, **L20,** 13
neoline structure, **L3,** 17
nomenclature, **8,** 360
α- and β-obscurine, structures, **L10,** 19
papilionaceous, **11,** 78
pithecolobine structure, **L16,** 11
sarpagine, carbon skeleton, detn. by mass spectrometry, **L15,** 9
selagine structure, **L10,** 26
proof, **L12,** 14
solanocapsin, absolute configuration at C-25, **L27,** 9
solanum, synthesis from 3β-acetoxy-5α-pregn-16-en-20-one, **L27,** 5
spermidine, from lunarine degradation, **L18,** 36
strychnine-curare, biogenetical laboratory synthesis, **L19,** 30
thelepogine, molecular structure and configuration of the methiodide, **L26,** 18
tylophorine structure, **9,** 53
vasicine synthesis according to Schöpf-oechler scheme, **L25,** 44
Zanthoxylum rhetsa DC, **8,** 293
Alkavinone structural relationship to pyrromycinone, **L8,** 28
Alkyl chlorides, α-elimination to cyclopropanes, **11,** 266
Alkyl groups, effect on absorption spectra of pyrilium salts, **9,** 167
electrical effects on an aromatic ring, **L15,** 1

Alkylation, of triphenylphosphin-alkenes, ketone synthesis, **L4,** 7
of triphenylphosphin-carbomethoxymethylen, acid synthesis, **L4,** 5
Alkyllithium derivatives, for synthesis of dialkyls and condensed thiophenes, **L6,** 30
Alkylmercuric compds., mechanism of isotope exchange reactions, **L19,** 7
Allantoic acid, fate and origin in plants, **L25,** 32
Allantoin, fate and origin in plants, **L25,** 32
Allenes, dissymmetric, configuration of (+)-3-methyl-3-t-butyl-1-chloroallene, **L8,** 16
Allylic alcohols, steroidal oxidation to $\alpha\beta$-unsaturated ketones, **L9,** 14
Aloe-emodin, synthesis, **L5,** 15
Aluminium, organometallic complexes, synthesis, **8,** 86
Aluminium chloride, catalysed reactions, **10,** 55
–nitromethane system, electron attraction by, **L9,** 5
1-Amidine-3-alkylureas, synthesis and reactions, **10,** 12
1-Amidine-3-arylureas, synthesis and reactions, **10,** 12
Amines, primary or secondary, reaction with salts of amidineureas, **10,** 12
reaction with dichlorocarbene, **11,** 1
Amino acids, configurations, quasi-racemate method, **8,** 129
thiazole synthesis, **L1,** 23
Amino groups, terminal, effect on electronic spectra of conjugated hydrocarbon systems, **10,** 109
Amino sugars, glycosides and oligosaccharides, synthesis, **99,** 116
α-**Aminoacetophenone** syn-oximes, *cis*-elimination during fragmentation, **L26,** 22
Aminoalkylsulphonic acids, and peptide analogues, syntheses, **9,** 289
4-**Aminoazobenzene** and derivatives, structures of mono-acid cations, **10,** 129
γ-**Aminopropyl chlorides,** transitions during solvolysis, **L23,** 25
Amylene, acetylation with various catalysts, **L2,** 7
Analgesics, hydrogenated quinolines and isoquinolines, **8,** 296, 304; **10,** 175
Androstane derivatives, total synthesis, **L17,** 27
Angustifoline, structure, **L19,** 1
Anionic bases, kinetics of bimolecular substitution in alcohol-water mixtures, **L24,** 1
Anisoles, substituted, steric enhancement of resonance, **L25,** 21
Annellation, asymmetric, in dibenzacenes, **9,** 202
Anthracene, conversion to + ion, **L9,** 5
derivatives, by reduction of anthraquinones, **L5,** 15
9,10-dibromo-, ozonation, effect of solvent, **L13,** 14
reaction with dichlorocarbene, **L7,** 27
Anthranil, MO-LCAO treatment, **10,** 81
Anthraquinones, action of diborane and of sodium borohydride-boron trifluoride-etherate, **L5,** 15
Anthraquinones (*continued*)
nucleophilic displacement reactions, **8,** 107
reduction to anthracene derivatives, **L5,** 15
Antibiotics, alkavinone, structural relationships to pyrromycinone, **L8,** 28
identity of pyrromycinone and rutilantinone, **L8,** 25
tetracycline, synthetic experiments, **11,** 52
Antimetabolites, γ-fluoroglutamic acid synthesis, **L14,** 21
Antimony compds., geometrical isomers of stibinous and stibinic propenyls, **L8,** 23
Antimony-pentaphenyl, prep., **10,** 12
Aromatic character, of cyclopenta [c] thiapyran, **L2,** 11
Aromatic compds., chlorination, effect of solvent on isomer distribution, **L13,** 9
hydrocarbons, reduction to mono-olefins, **L16,** 1
stability, significance of benzenoid rings, **10,** 171
maleic anhydride addition, **L21,** 1
polycyclic, ozonation, effect of solvent, **L13,** 14
polyfluoro, **8,** 38
prep. of + ions, **L9,** 5
substitution, effect of substituents, **L15,** 1
with 2 boron atoms, **L23,** 8
Aromatic systems, monohetero-, six-membered monocyclic, absorption spectra, **9,** 163
non-benzenoid, MO calculations, **11,** 121
prediction by Craig's rule, **11,** 121
tropilium salts and benzene, interconversions, **8,** 33
Artemisin, correlation with santonin, **8,** 186
4-**Arylcycloalk-2-en-1-one** series, experiments, **11,** 154
Aryllithium derivatives, for synthesis of diaryls, and condensed thiophenes, **L6,** 30
Arynes, structure, **9,** 29
Aspidosperma australe, alkaloids, **L1,** 18
Asymmetric annellation effects dibenzacenes, **9,** 202
Asymmetric synthesis, of sulphoxides, **L6,** 20
Auranetin, 5-hydroxy-, from *citrus aurantium,* **8,** 64
8-**Aza-des-N-morphinan,** N-methyl, steric structure, **8,** 304
synthesis, **8,** 296
N-methyl-3-hydroxy-, synthesis, **10,** 175
1-**Azo-bis-1-phenylethane,** thermal decomposition, acceleration by chloranil, **L23,** 18
Azo compds., aromatic, reactions, absorption spectra and resonance structures, **9,** 194
Azobenzene, photocatalysed cyclization, **L9,** 12
Azoferrocene, prep. **L1,** 1
Azoic coupling components, constitution. **11,** 140
Azomethin-imines, 1,3-dipole additions, **L12,** 5
zwitterion compds., **L12,** 1
Azonium ion, of 4-aminoazobenzene, **10,** 129
Azulenes, reactions with triphenylmethyl perchlorate, **L27,** 3

Basicity of indoles, position, **L21,** 12
Beckmann rearrangements, of *o*-alkylbenzophenones, **9,** 210
Benzene, chlorination, effect of solvent, **L13,** 9
conversion to tropilium cation, **8,** 33
derivatives, bond lengths, **8,** 13
maleic anhydride addition, **L21,** 1
tetra-, penta- and hexa-fluoro-, prep., **9,** 240
Benzenoid rings, significant for stability of aromatic hydrocarbons, **10,** 171
Benzilidene aniline, hydrolysis in presence of cationic detergent salt, **L1,** 7
Benziminazole, mechanism of formation, **8,** 79
Benzisoxazoles, MO-LCAO treatment, **10,** 81
6,7-**Benzocoumaran-2-ones,** substituted, prep., **11,** 158
Benzologues of peropyrene, **10,** 26
Benzophenone, photochemical interaction with isopropyl alcohol and nitric oxide, **8,** 350
photosensitized, maleic anhydride addition to benzene and aromatic compds., **L21,** 1
Benzophenones, *o*-alkyl-, Schmidt reaction, oximation and Beckmann rearrangement to amides, **9,** 210
Benzoquinone, 2,3-dichloro-5,6-dicyano-, oxidation reagent for steroidal allylic alcohols, **L9,** 14
p-**Benzoquinone,** tetra- and tri-fluoro, prep., **8,** 38
Benzotriazoles, formation, **8,** 79
Benzoxazine derivatives, prep. and structure, **11,** 133
Benzyl chloride, reaction with N-butyllithium, **L24,** 26
Benzyl ethers, copper salt catalysed reactions with t-butyl perbenzoate, **L2,** 4
Benzyl ketones, Stobbe reaction, **11,** 158
Benzylaminoalkylsulphonic acids, syntheses, **9,** 292
Benzyne, formation from fluorobenzene, action of lithium piperidide, **9,** 29
Bicyclanes, part II, **9,** 230
Bicyclo [2.2.0]-**hexane,** photochemical synthesis, **L21,** 24
Bicyclo [2,2,2,] **octane,** prep. and halogenation, **9,** 230
Bicyclo [3,2,1] **octene**-2, structure, **9,** 231
Biguanides, alkyl or aryl, hydrolysis, **10,** 12
Biogenesis, concept for laboratory synthesis of cyclic compds., **L12,** 27
formation of sugiol and nimbiol, **10,** 45
hyoscine in *Datura stramonium* L., **L22,** 1
laboratory synthesis in strychnine-curare alkaloid series, **L19,** 30
lycopodium alkaloids, **L10,** 34
Bisborazaro compds., formation, double cyclizations of diamines, **L23,** 8
Bis-(trimethylene)-ferrocene, synthesis, **L7,** 4
Bond energies, calculation for hydrocarbons, **11,** 117
carbon-carbon, **9,** 65
Bond lengths, butadiene, **11,** 111
in benzene derivatives, **8,** 13
in conjugated systems, **11,** 96
Bonds, C-H, with different dissociation energies, reaction with chlorine atoms, **8,** 101
new C-C, biogenetic concept for formation in cyclic compds., **L12,** 27
peptide, synthesis, **L14,** 9
Borepin, synthesis, **L8,** 14
1-**Boro**-2,4,6-**cycloheptatriene,** *see* Borepin.
Borohydride-boron trifluoride, action on anthraquinones, **L5,** 15
Boron compds., with 2B atoms, **L23,** 8
Boron trifluoride etherate, induced fission reactions of steroid 5,6,-epoxides, **8,** 116
Bromination, of isoquinoline, mechanism **8,** 23
Bulnesol, structure, **L11,** 18
Butadiene, bond lengths, **11,** 111
Butene, *cis* and *trans*, reaction with methyl diazoacetate, **10,** 65
(+) 3-*t*-**Butyl**-1-**chloroallene,** 3-methyl-, absolute configuration, **L8,** 16
t-**Butyl hydroperoxide,** deoxygenation with O_3, **L14,** 1
t-**Butyl perbenzoate,** copper salt catalysed reactions with benzyl ethers, **L4,** 4
N-**Butyllithium,** reaction with benzylchloride, **L24,** 26
2-**Butyne,** addition of methylene and carbomethoxycarbene, **10,** 65
2-**Butyn**-1,4-**diol-polymethylene ether,** synthesis, **L17,** 5

(±)-**Cadinene dihydrochloride,** synthesis, **L27,** 27
Calycanine, synthesis, **8,** 291
Camphor, formation mechanism, from homocamphoric acid, **L2,** 19
reduction to isoborneol by metals **L21,** 16
DL-**Canaline,** amino-oxy peptide derivatives, **L18,** 28
Cannabidiol, separation from hashish components, **10,** 153
Caranine, lycorine, pluvüne and lycorenine, configurational relationship, **11,** 89
Carbazoles, synthesis, **8,** 73, 79; **10,** 230
Carbomethoxycarbene, addition to butyne-2, **10,** 65
Carbon 14, reaction study, of isocyanates and acid anhydrides, **L2,** 15
pyrolytic decarboxylation of acids, **L2,** 19
Carbon-carbon bond energies, **9,** 65
Carbon dioxide, reduction with ^{60}Co-γ-radiation, **L18,** 17
Carbon monoxide and N_2, hybridization of *s* and p^σ orbitals, interpretation of chemical properties, **10,** 212
reaction with cycloalkanes, **10,** 55
Carbon tetrabromide, reaction with enol ethers of Δ^4-3-ketosteroids, **9,** 149
Carbohydrates, carboxyl groups, diborane reduction, **L7,** 17
Carbonium ions, homocyclopropenyl, an octahydrodimethanonaphthylcation, **L25,** 4
mesomeric, behaviour, **L16,** 17
unsymmetrically substituted, apportionment of products, **L16,** 17

Carbonium ions (*continued*)
reactions, ionization-dissociation of chlorobenzhydryl chloride in acetone **L2,** 31
of ferrocene derivatives, role of Fe, **L13,** 1
Carbonyl derivatives, aliphatic, substituent and solvent effects on $n \rightarrow \pi$ ($^1U \rightarrow {}^1A$) transition, **L2,** 1
Carboxyl groups, carbohydrate, reduction with diborane, **L7,** 17
Carcinogenesis, by thiophene isoesters of polycyclic hydrocarbons, **9,** 76
Carissone, configuration, **8,** 183
Carotol, structure, **8,** 271
Casimiroa edulis lave *et* ex, constituents, **9,** 139
Catalysis, intramolecular alkaline hydrolysis of alicyclic 1,2-diol monoesters, **L24,** 22
Catalysts, copper salt, t-butyl perbenzoate reaction with benzyl ethers, **L2,** 4
platinum, oxidation of alcohols, **9,** 67
various, in amylene acetylation, **L2,** 7
Ziegler-Natta, formation of isotactic polypropylene, **L17,** 17
reaction mechanism in ethylene polymerization, **L17,** 12
Cations, mono-acid, of 4-aminoazobenzene and derivatives, **10,** 129
Cetyltrimethylammonium bromide, benzilidene aniline hydrolysis in presence of, **L1,** 7
Cevine, configuration, X-ray study, **L7,** 24
Chloranil, condensation with 3,4-dimethoxyphenol, **10,** 135
Chloride exchange, in solvolysis of *p*-chlorobenzhydryl chloride, **L22,** 12
Chlorination, nuclear of perchlorostilbenes, **9,** 156
of aromatics, effect of solvent on isomer distribution, **L13,** 9
Chlorine atoms, reactions of, separation of polar and resonance effects, **8,** 101
p-**Chlorobenzhydryl chloride,** racemization and radio-Cl exchange in acetone, **L2,** 31
solvolysis, ion pairs, racemization, chloride exchange and mass law effect, **L22,** 12
Chloroisoretamine, 11-chloro-(+)-α-isosparteine structure, **11,** 78
Chlororetamine, 8-chloro-(+)-sparteine, **11,** 78
Chlorosilanes, organic di- and tri-, synthesis of di- and tri-fluorosilanes, **L5,** 11
5α-**Cholestane** derivatives, contraction of ring A, **11,** 199
Chromanone lichen acid, proposed structure, **L4,** 1
Chromatography, paper, identification of tetrahydrocannabinol, **10,** 153
vapour phase, components of cigarette smoke, **11,** 11
Cigarette smoke, chemistry, **11,** 11
Citral, thermal isomerization, **L11,** 10
Citreorosein, synthesis, **L5,** 15
D-**Citronellal,** synthesis from, of iridolactone, analogues **9,** 295
Citrullus vulgaris, isolation and structure of α-amino-β-(pyrazolyl-N)-propionic acid, **11,** 231
Citrus aurantium, new components, **8,** 64
Cobalt, ^{60}Co-γ-radiation, Co_2 reduction, **L18, 17**
Codeine, tyrosine incorporation, rate study, **L27,** 21
Complexes, molecular, absorption spectra, **10,** 96
organometallic, of titanium and aluminium, syntheses, **8,** 86
Configuration, estrogenic activity and non-planar structure of substituted ethylenes **8,** 205
quasi-racemate method, **8,** 126
Conformation, D-ring in D-homosteroids, **11,** 213
of organic molecules, calculation, **9,** 183
Conjugated systems and resonance, **11,** 96
Conjugation in cycloöctadecanonaene, **L11,** 22
Corticoids, 16-methylene, synthesis, **L16,** 21
Costunolide, structure, **9,** 275
Craig's rule for predicting aromaticity, **11,** 121
Cucurbitacin B, ring A, NMR spectra, **L15,** 15
stereochemistry, **L22,** 23
structure, **L14,** 13
Cucurbitacins, stereochemistry, **L22,** 23
Cumene, autoxidation, termination mechanism, O^{18} tracer evidence, **L24,** 30
DL-**Cuparene,** synthesis, **L23,** 14
Cuprenene, isolation from *Thujopsis dolabrata,* **L23,** 14
Cupressales, sesquiterpenes, **9,** 237
Curare alkaloids, biogenetic laboratory synthesis, **L19,** 30
Cyanoguanidine, reaction with alkyl or aryl amines, **10,** 12
Cyanuric chloride, condensation with *o*-hydroxybenzanilide, **11,** 133
Cyclasteroids, irradiation of 20-ketosteroids, **L4,** 10
Cyclic compds., synthesis, biogenetic concept, **L12,** 27
Cyclization, double, from diamines, formation of bisborazaro compds., **L23,** 8
Finkelstein, dimerization, **L24,** 13
photocatysed, of azobenzene, **L9,** 12
Cycloaliphatic ketones, catalysed reactions with diazomethane, **L13,** 30
Cycloalkanes, conformational analysis, **9,** 40
reaction with CO, **10,** 55
Cycloalkenes, conformational analysis, **9,** 40
Cyclobutadiene silver nitrate, I.R. spectrum, **L26,** 35
Cyclobutane derivatives, of maleic and fumaric acids, **L3,** 13
Cyclobutane-1,2-dicarboxylic acid photosynthesis of bicyclo [2.2.0]-hexane, **L21,** 24
Cyclobutanol, isomerization, **11,** 171
3,8-**Cyclodecadiyne,** 1,6-dioxa-, prep., **L26,** 25
Cycloheptatriene, formation from tropylium ion, hydride transfer reactions, **L21,** 20
7-**Cycloheptatrienylmethyl** ammonium iodide, trimethyl, Hofmann elimination to heptafulvene, **11,** 183
1,3-**Cyclohexadiene,** condensation with ethylene, **9,** 230

Cyclohexadienone, acid stable, **L7,** 12
Cyclohexane-2-acetic acid, 1,3-dimethyl-1,3-dicarboxy-, synthesis, **11,** 234
Cyclohexanecarboxylic acids, prep., **10,** 55
with equatorial and axial carboxyl groups, apparent p*K* values, **L20,** 18
Cyclohexyl methyl ketone, prep., **10,** 55
Cyclohydration, of diphenyltrifluoromethylcarbinols, **11,** 252
Cycloöctadecanonaene, bond alternation in, **L11,** 22
molecular deformation, **11,** 125
Cyclopentadienyltrimethyltitanium, prep., **L14,** 19
Cyclopentane, conformation, **L1,** 3
reaction with CO, **10,** 55
Cyclopenta [c] **thiapyran,** electrophilic substitution, aromatic character and structure evidence, **L2,** 11
Cyclopropanes, from alkyl chlorides by α-elimination, **11,** 266, 272
Cyclopropenes, from carbenes and acetylenes, **10,** 65
rearrangements, **L26,** 42
Cyclopropylcarbinol, isomerization, **11,** 171
Cyclopropylcarbinyl chloride, solvolysis, **11,** 171
2,6,10-**Cycloundecatriene-1-one,** 2,6,9,9-tetramethyl-, structure of zerumbone, **8,** 171
Cyperones, configuration, **8l** 183
Cytopyrrolic acid, synthesis, **8,** 266

Dacrydium biforme, isopimaric acid from, **8,** 356
Datura stramonium, hyoscine biogenesis in, **L22,** 1
Daucus carota, carotol structure, **8,** 271
Debromination, of vic-dibromides with diaryltellurides, **L15,** 5
Decalin, reaction with CO, **10,** 55
trans-trans-1-**Decalin-carboxylic acid,** prep., **10,** 55
(±)-*trans*-**Decalin-1,6-dione,** 4-isopropyl, total synthesis, **L27,** 27
Dehydroabietic acid, synthesis of 2 stereoisomers **L23,** 1
16-**Dehydropregnenes,** 12-keto-, conversion to 12-methyl hemiketals, **10,** 238
Delphinine, configuration, **L15,** 23
structure, **9,** 254
2-**Deoxy-D-glucose,** 2-(2′,4′-dinitrophenyl)-amino, and derivatives, reactions, **9,** 116
Deoxygenation, t-butyl hydroperoxide reaction with O_3, **L14,** 1
Desdimethylaminoterrarubein, synthesis, **11,** 52
Desmethylnobiletin, isolation from orange peel, **8,** 64
3-**Desoxyequilenin,** pyrrolo analogues, attempted synthesis, **10,** 230
Detergent salts, cationic, benzilidene aniline hydrolysis in presence of, **L1,** 7
Deuterium, effects, and mass sensitive amplitudes of vibration **L6,** 13
in aromatic halogenation of polyalkylbenzenes, **L23,** 30
in D_2O-H_2O-mixtures, **10,** 200
Deuterium (*continued*)
in $KMnO_4$ oxidation of phenyltrifluoromethyl carbinols, **L2,** 28
structure difference between light and heavy water, **10,** 182
Dialkyls, synthesis, **L6,** 30
Diamond, carbon-carbon bond energies, **9,** 65
Diaryliodonium, cation, reaction with dimedone, dibenzoyl- and tribenzoyl- methane, **8,** 49
Diaryls, synthesis, **L6,** 30
Diaryltellurides, reaction with vic-dibromides, **L15,** 5
α-**Diazoacetophenone,** reactions with sodium methoxide and with pot. t-butoxide, **L17,** 22
Diazoacetophenones, *p*-substituted, infra-red intensity measurements, **11,** 285
Diazo-compounds, aromatic, structure, **11,** 30
infra-red intensity measurements, **11,** 285
Diazohydrocarbons, aromatic, infra-red intensity measurements, **11,** 285
Diazomethane, reaction with cycloaliphatic ketones, **L13,** 30
reaction with α,β-unsaturated ketones, **L5,** 1
Dibenzacenes, asymmetric annellation effects, **9,** 202
Dibenzodiphenylene and *cis*-isomer, π electron energies and bond orders, **10,** 41
4,5:12,13-**Dibenzoheptazethrene,** synthesis, **9,** 96
Dibenzo [a,i] **pyrene,** synthesis, **8,** 1
Dibenzoylmethane, phenylation, **8,** 49
Diborane, action on anthraquinones, **L5,** 15
reduction of carboxyl groups in carbohydrates, **L7,** 17
Dibromides, vicinal, reaction with diaryltellurides, **L15,** 5
2,4-**Dibromomenthone,** structure, **11,** 219
2,6-**Di-t-butylpyridine-3-sulphonic acid,** synthesis and structure, **L1,** 13
2,6-**Di-t-butylpyridine-4-sulphonic acid,** synthesis and structure, **L1,** 13
Dichlorocarbene, reaction with amines, **11,** 1
reaction with anthracene, **L7,** 27
Dichlorodiphenylsilane, reaction with Na and with Li, formation of dodecaphenylcyclohexasilane, **L23,** 5
Dicyclopentadiene series, isomerizations, **L11,** 5
Dicyclopentadienyliron *see* Ferrocene.
Diels-Alder, 1,3-cyclohexadiene and ethylene condensation, **9,** 231
Diethylenic acids, fission in strong alkali, **8,** 239
Dihydrocuparene, *see* Cuprenene
5,12-**Dihydronaphthacene,** 2,4,6-trihydroxy-5-oxo-, synthesis, **11,** 52
Dihydropentalenyl derivatives, synthesis, **L18,** 31
Dihydrotoxiferine, structure, **L26,** 1
Di-indolylmethenes, condensation with homo- and hetero-cyclic aldehydes, **9,** 111
formation from indoles, and synthesis, **9,** 111
Dimedone, phenylation, **8,** 49
Dimerization, in Finkelstein cyclizations, **L24,** 13
of N-methyl-2-pyridone, **L25,** 1
Dimers, skatole, structure, **L26,** 13
Dimesityl disulphide, photolysis, **10,** 76

3,4-**Dimethoxyphenol,** condensation with chloranil, **10,** 135
cis- and *trans*-**Di-*p*-methoxystilbene** structure and estrogenic activity, **8,** 205
(−)*trans*-1,2,-**Dimethylcyclopropane,** absolute figuration, **11,** 272
1,2-**Dimethylcyclopropene,** prep., **10,** 65
1,2-**Dimethylcyclopropene**-3-**carboxylate,** prep., **10,** 65
Δ^2-3,10-**Dimethyl**-6-**isopropylbicyclo**-(0,3,5)-**decen**-6-**ol**, carotol structure, **8,** 271
1,1-**Dinitroalkane anions,** substituent effects in charge-resonance spectra, **L27,** 17
2,4-**Dinitrobenzenesulphenyl chloride,** reaction with organic monosulphides, **9,** 58
2,4-**Dinitrochlorobenzene,** condensation with *o*-hydroxyarylamides, **11,** 140
Dioscorea tokoro, kogagenin structure, **10,** 1
Diphenyl *p*-nitro *p'*-amino derivatives, electronic spectra and interpretation, **10,** 109
Diphenylamine, chromic acid oxidation, **8,** 322
Diphenylamines, conversion to 2- and 4- trifluoromethylcarbazoles, **8,** 79
Diphenylcyclopropene carboxylic acid, formation of 2,3,5-triphenylfuran from, **L26,** 42
Diphenylenes, substituted, stability, **10,** 41
β,β-**Diphenylethyleneazobenzene,** indole ring formation from, **L7,** 33
Diphenylethylenes, unsymmetrical, estrogenic activity, **8,** 205
Diphenylglycolaldehyde phenylhydrazone, dehydration to β,β-diphenylethyleneazobenzene, **L7,** 33
Diphenylmethane, chronic acid oxidation, kinetics, **8,** 313
Diphenyls, conversion to 2- and 4- trifluoromethylcarbazoles, **8,** 73
Diphenyltrifluoromethylcarbinols, cyclohydration, **11,** 252
Diquinones, oosporein-tomichaedin degradation **10,** 148
Diskatole, structure, **L26,** 13
Dissociation constants, apparent, of cyclohexane carboxylic acids with equatorial and axial positions of carboxyl group, **L20,** 18
Dissociation, triphenylchloromethane in nitrobenzene, **L18,** 10
Disulphides, aromatic, photolysis, **10,** 76
Ditellurides, halogenolysis, **11,** 15
Diterpenoids, ring C substitution in pimaric acids, **L25,** 37
DNP-D-Glucosamine, and derivatives, reactions, **9,** 116
Dodecaphenylcyclohexasilane, formation from dichlorodiphenylsilane, **L23,** 5
Dyes, cyanurated, **11,** 133
trinuclear indole, synthesis, **9,** 106, 111

Echitamine, constitution, **L10,** 10
3 proposed structures, criticism, **L19,** 36
structure, **L6,** 1; **L11,** 25
Elatericin A and B, stereochemistry, **L22,** 23
Elaterin, stereochemistry, **L22,** 23
Electrons, acceptors, Lewis acid-nitro compd. system, **L9,** 5
correlation in conjugated molecules, **11,** 112
donors and acceptors, absorption spectra of molecular complexes, **10,** 96
Electrophilic substitution, in cyclopenta [c] thiapyran, **L2,** 11
isoquinoline, **8,** 23
Elimination reactions, E_2, effect of leaving group on orientation, **L18,** 1
α-**Elimination,** of alkyl chlorides to give cyclopropanes. **11,** 266
Cis-**Elimination,** during fragmentation of *syn*-α-aminoaceto-phenone oximes, **L26,** 22
Elymoclavine, biosynthesis, **L7,** 1
Enantiomorphs, steric correlation, quasi-racemate method, **8,** 129
Energy, and molecular geometry in alicyclic systems, **9,** 40
for C-C bonds, **9,** 65
interaction, of non-bonded atoms, detn. by molecular structural analysis, **9,** 183
16α, 17α-**Epoxides,** steroidal, ring opening, **L17,** 34
Equilenin pyrrolo analogues, attempted synthesis, **10,** 230
Equilibrium, between thiocyanates and isothiocyanates, **L11,** 27
cis-trans of α-hydrindanones, effect of structure, **L18,** 4
Eremophilone, stereochemistry, **8,** 203
Ergosterol, and photoisomers, emission spectra, **11,** 276
Ergot alkaloids, biosynthesis, **L7,** 1
Erythrinan alkaloids, stereochemistry, **L14, 5**
Estrogenic activity, and molecular structure, **8,** 205
Estrogens, molecular structure and activity, **8,** 150
Estrone, stereoselective synthesis, **L5,** 20
Ethers, introduction of benzoyloxy group, **L2,** 4
Ethylene, condensation with 1,3-cyclohexadiene, **9,** 230
polymerization, **8,** 86
reaction mechanism with Ziegler-Natta catalysts, **L17,** 12
Ethylenes, formation from *vic*-dibromides and diaryltellurides, **L15,** 5
substituted, estrogenic, variation in planarity, **8,** 205
Ethylenic acids, fission, **8,** 221, 239, 246
Eudesmane, stereochemistry, **8,** 181
Eudesmol, configuration, **8,** 182
Evodiamine, isolation, **8,** 293

Ferrocene derivatives, carbonium ion reactions, role of Fe, **L13,** 1
Ferrocenes double bridged, synthesis, **L7,** 4
Finkelstein cyclizations, dimerizations, **L24,** 13
Flavone, 2',5,6-trimethoxy-, 2',5,6,7-tetramethoxy- and 5-hydroxy-2',6,7-trimethoxy-, from *Casimiroa edulis*, **9,** 139
Flavonoids, from *Casimiroa edulis*, **9,** 139
5-hydroxyauranetin from *Citrus aurantium*, **8,** 64
nomenclature, **8,** 336

Fluoradene, acidity, LCAO treatment, **L6,** 23
Fluorene derivatives, formation, **11,** 252
Fluorine, *cis*-addition to steroid olefin, **L20,** 34
Fluorine compds., 2- and 4-trifluoromethyl-carbazoles, syntheses, **8,** 73, 79
organic, mevalolactone derivatives, **L8,** 20
perfluorovinyl derivatives of tin and silicon, reaction with organolithium reagents, **L22,** 20
polyfluoro-aromatic, **8,** 38
tri- and tetra-fluoro-*p*-benzoquinone, **8,** 38
tetra-, penta- and hexa-fluorobenzenes, prep., **9,** 240
toxic with C-F link, **10,** 160
trifluorolaevulic acid and derived compds., **10,** 164
2-Fluoroethanol, lability of the fluorine atom, **10,** 160
γ-Fluoroglutamic acid, synthesis, **L14,** 21
Fluorosilanes, organic di- and tri-, synthesis, **L5,** 11
Formolysis, of ozonides, formation of peracids, **L26,** 34
Formylation, condensed aromatic hydrocarbons, **8,** 7
Free-radicals, reactions involving sulphur compounds, **10,** 76
reactions with atoms, solvent effects, **8,** 101
Fumaric acid, photodimerization to cyclobutene derivatives, **L3,** 13
Fungi, isolation of gibberellin A_7, **L15,** 18
pigments, part XII, **10,** 135

α-D-Galactopyranosiduronic acid, reduction, **L7,** 19
Galactosyl-lactose, structure, **9,** 125
Gelsemine, degradation, **11,** 148
Gentiopicroside, structure, **L24,** 7
Gentrogenin, sidechain degradation, **10,** 238
Gibberellin, A_5, structure, **11,** 60
Gibberellin A_7, fungal gibberellin, **L15,** 18
Gibberellin A_9, isolation and structure, **L23,** 22
Gibberellins, A_1 and A_5, isolation from *Phaseolus multiflorus*, **11,** 60
Glycerophosphatides, synthesis of "mixed-acid" α-lecithins, **L9,** 1
Glycosides, nitrogen, of substituted rhodanines, **L6,** 10
of amino sugars, synthesis, **9,** 116
turbicoryn from *Turbina corymbosa*, **L7,** 30
Graphite, carbon-carbon bond energies, **9,** 65
Gross equation, parameters in H_2O-D_2O mixtures, **10,** 211
Guaiol, absolute configuration, **L22,** 33
stereochemistry, **L11,** 18
Guatambuine, *see* U-alkaloid C. **L1,** 18

Halogen salts of thiapyrylium, synthesis, **L23,** 11
Halogenation, aromatic, of polyalkylbenzenes, reaction selectivity, hydrogen isotope effect and steric hindrance, **L23,** 30
of bicyclo [2,2,2] octane, **9,** 230
Hammett equation, application to theory of tautomeric equilibrium, **9,** 10
Heats, of formation, in conjugated systems, **11,** 96
Hecogenin, sidechain degradation, **10,** 238
Hemiketals 12-methyl-, from 12-keto-16-dehydropregnenes, **10,** 238
Heptadecanoic acid, 5-oxo-, alkali fusion, **8,** 251
10-oxo- alkali fusion, **8,** 250
1H-Heptafluorocyclohexa-1,4-diene, reaction with oleum, **8,** 38
Heptafulvene, synthesis and hydrogenation to methylcyclo-heptane, **11,** 183
Heterocyclic compds., five membered, molecular orbital treatment, **8,** 23
formation from α-diazoacetophenone, **L17,** 22
oxygen, structure of sophorol, **L19,** 16
steroids, synthesis, **10,** 215, 223, 230
ten-membered diacetylene, synthesis, **L26,** 25
Heterocyclic systems, borepin synthesis, **L8,** 14
Hexadecanoic acid, 9,10,16-trihydroxy-, alkali fusion, **9,** 251
trans- **Hexahydro-α-benzosuberone,** prep., **10,** 55
Hexahydroxynaphthaquinone, spinochrome E structure, **L1,** 11
Hofmann rule, effect of leaving group on orientation in E_2 eliminations, **L18,** 1
D-Homoannulation, of 17-hydroxy-20-keto steroids, **11,** 163
Homocamphoric acid, mechanism of camphor formation, **L2,** 19
D-Homoketolic systems, equilibrium relationship, **11,** 163
Homologous series, cycloaliphatic ketones, syntheses, **L13,** 30
hydrocarbons, direct nucleophilic substitution, **L12,** 18
reaction of diazomethane with αβ-unsaturated ketones, **L5,** 1
D-Homosteroids, boat conformation of D-ring, **11,** 213
contraction of 6- to 5-membered rings, **11,** 199
Hormones, 19-hydroxy-10-isotestosterone synthesis, **L22,** 38
8-isotestosterone total synthesis, **L12,** 23
DL-18-nortestosterone synthesis, **L8,** 11
plant, **11,** 60
synthesis of 16-methylene corticords and progesterones, **L16,** 21
Humulene, structure, **9,** 1
Hybridization in benzene derivatives, **8,** 13
in conjugated systems, **11,** 96
in CO, **10,** 212
Hydration, ionic, in D_2O–H_2O mixtures, **10,** 200
in D_2O and H_2O, **10,** 188
Hydride hyperconjugation, in 1(3)-methazulenes, **L27,** 1
Hydride transfer reactions, **L21,** 20
α-Hydrindanones, structural effects on *cis-trans* equilibrium **L18,** 4
Hydroboration, of β-pinene, **L21,** 9

Hydrocarbon chains, direct nucleophilic substitution, transmission of polar effects, **L12,** 18
Hydrocarbons, acidity, LCAO treatment, **L6,** 23
aromatic, condensed, formylation, **8,** 7
formation of + ions, **L9,** 5
reduction to mono-olefins, **L16,** 1
conjugated, effect of terminal NO_2 and NH_2 groups on electronic spectra, **10,** 109
heats of formation, **11,** 107
non-benzenoid, synthesis of heptafulvene, **11,** 183
polycyclic, carcinogenic thiophene isoesters, **9,** 76
synthesis of tetradecahydro-octahydro- and dihydro-dibenzoheptazethrenes, **9,** 96
Hydrogen cyanide, tetramer, structure, **L6,** 17
Hydrolysis, kinetics of bimolecular substitution by anionic bases in alcohol-water mixtures **L24,** 1
Hydronium ions, solution in H_2O and D_2O, **10,** 197
Hydroperoxides, organic, reaction with ozone, **L14,** 1
Hydroxide ions, solution in H_2O and D_2O, **10,** 197
o-**Hydroxyarylamides,** condensation with 2,4-dinitrochlorobenzene, **11,** 140
o-**Hydroxybenzanilides,** condensation with cyanuric chloride, **11,** 133
α-**Hydroxybutyraldehyde,** γ-amino-, synthesis, application to synthesis of vasicine, **L25,** 44
cis-10-**Hydroxydec-2-enoic acid,** synthesis, **L13,** 34
trans-10-**Hydroxy-dec-2-enoic acid,** synthesis, **L4,** 15
2-**Hydroxyestradiol-17**β′, synthesis, **10,** 144
8α-**Hydroxylabd-13-ene,** hydrogenolysis, **10,** 71
Hydroxylycoctonine, structure and chemistry, **9,** 284
4-**Hydroxypiperidines,** conformation, **L14,** 23
Hyoscine, biogenesis in *Datura stramonium* L., **L22,** 1
Hyperconjugation, hydride, in 1(3)-methazulenes, **L27,** 1
in excited states of molecules, **L2,** 1
Humulinone, structure, **9,** 271
Humulene, correlation with zerumbone, **8,** 171

Iminoacetonitrile, HCN tetramer structure, **L6,** 17
Indole dyes, **9,** 106, 111
ring, formation from β,β-diphenylethylene-azobenzene, **L7,** 33
Indole trimethincyanines, condensation with heterocyclic aldehydes, **9,** 106
Indoles, position of protonation and basicities, **L21,** 12
Indoline derivatives, new reactions, **L26,** 13
Indolopyridone, synthesis, **L11,** 15
Indolopyrone, synthesis, **L11,** 15
Indoxazene, MO-LCAO treatment, **10,** 81
Insecticides, ryanodine, skeletal structure, **L15,** 31
Ion pairs, in bimolecular nucleophilic substitution **L9,** 24
in solvolysis of *p*-chlorobenzhydryl chloride, **L22,** 12
Ionization, tautomeric compds., application of Hammett equation, **9,** 12
triphenylchloromethane derivatives in nitrobenzene, **L18,** 10
Ionization-dissociation, of chlorobenzhydryl chloride in acetone, **L2,** 31
Ions, hydration, in D_2O and H_2O, **10,** 188
in D_2O–H_2O mixtures, **10,** 200
monatomic, solutions in D_2O and H_2O, heat content, entropy and free energy, **10,** 182
monovalent +, formation, **L9,** 5
Iridolactones analogues, synthesis, **9,** 295
Iridomyrmecins, steriochemistry, **L11,** 18
Irigenins, synthesis, **L5,** 6; **L20,** 23
Iron, role, in carbonium ion reactions of ferrocene derivatives, **L13,** 1
Isoborneol, by metallic reduction of camphor, **L21,** 16
Isobutyl chloride, α-elimination to methylcyclopropane, **11,** 266
Isocyanates and acid anhydrides, reaction investigation with ^{14}C, **L2,** 15
Isoflavanones, structure of sophorol, **L19,** 16
Isoflavone, 5,7-dihydroxy-6-methoxy-derivatives, synthesis, **L5,** 6
Isolongifolene, prep., **8,** 42
Isomerism, *cis-trans* of steroidal $\Delta^{17(20)}$ enol acetates, **8,** 145
geometrical of diaryl ketimine derivatives, interplay of steric and electronic factors, **9,** 210
Isomerization, in dicyclopentadiene series, **L11,** 5
of cyclopropylcarbinol and cyclobutanol, **11,** 171
photochemical, of provitamin D, **11,** 276
thermal and, catalysed of chlorinated α,α′-dichlorostilbenes, **9,** 156
thermal of citral, **L11,** 10
of thiocyanates and isothiocyanates, **L11,** 27
Isomiropinic acid, identification, **8,** 356
Isomyrtanol, formation from β-pinene, **L21,** 9
Isophyllacladene, from mirene, **L24,** 18
reaction with Prevost reagent, **L17,** 9
structure, **8,** 261
Isopimaric acid, identity of miropinic acid, **8,** 356
Isoquinoline, molecular orbital treatment, **8,** 23
Isoquinolines, hydrogenated, as analgesics, **8,** 296, 304, **10,** 175
Isoretamine, 8-hydroxy-(+)-sparteine epimer, **11,** 78
(+)-α-**Isoparteine,** 11-chloro-, chloroisoretamine structure, **11,** 78
8-**Isotestosterone,** total synthesis, **L12,** 23
10-**Isotestosterone,** 19-hydroxy-, synthesis **L22,** 38
Isothiocyanates and thiocyanates, equilibrium, kinetics and isomerization mechanism, **L11,** 27

Isotopes, exchange reactions of alkylmercuric and dialkylmercury halides, **L19,** 7
O^{18} tracer evidence, termination mechanism in autoxidation of cumene, **L24,** 30
secondary effects and mass sensitive amplitudes of vibration, **L6,** 13
solvent effects, for H_2O-D_2O mixtures, **10,** 200
of D_2O and H_2O, **10,** 182

Jacobine bromhydrin, molecular structure and absolute configuration, **L23,** 35
Jatamansone, indentity with valeranone, **L3,** 9
Junipene, identical with kuromatsuene and longifolene, **9,** 237
Juniperol, identical with kuromatsuol, macrocarpol and longiborneol, **9,** 237

K-bands, conjugated hydrocarbon systems, effect of terminal NO_2 and NH_2 groups, **10,** 109
p-polyphenyl series, effect of *para*-substituents, **10,** 102
thiobenzophenone, effect of substituents, **10,** 119
Kaurene, structure, **L24,** 18
Ketimine derivatives, diaryl, geometrical isomerism, interplay of steric and electronic factors, **9,** 210
8-**Ketodicyclopentadiene,** rearrangement, **L22,** 29
Ketones, cycloaliphatic, catalysed reactions with diazomethane, **L13,** 30
from catalytic oxidation of secondary alcohols, **9,** 67
from phyllocladene, **11,** 226
reactions in strong alkali, **8,** 246
synthesis, C-alkylation of triphenyl-phosphinalkenes, **L4,** 7
Schmidt reaction, mechanism, **9,** 210
α,β-unsaturated, reaction with diazomethane, **L5,** 1
Ketophenol, nimbiol structure, **10,** 45
20-**Ketopregnanes,** formation from, of *gem*-methoxy hydroperoxy compds., **9,** 145
$\Delta^{4,3}$-**Ketosteroids,** enolethers, reaction with polyhalomethanes, **9,** 149
6α-methyl-, synthesis and biological activity, **9,** 149
20-**Ketosteroids,** photochemical reactions, **L4,** 10
syn-**Ketoximes,** α-aminoacetophenone, *cis*-elimination during fragmentation, **L26,** 22
Kinetics, chromic acid oxidation of diphenylmethane, **8,** 331
controlled carbonium ion reactions, products formed, **L16,** 19
of benzilidene aniline hydrolysis in presence of cationic detergent salt, **L1,** 7
of bimolecular substitution by anionic bases in alcohol-water mixtures, **L24,** 1
thiocyanate and isothiocyanate isomerization, **L11,** 27
Kunomatsuene, identical with junipene and longifolene, **9,** 237
Kunomatsuol, identical with juniperol, macrocarpol and longiborneol, **9,** 237

Lactams, α,β-unsaturated, photodimerization, **L25,** 1
Lactose, action of *Penicillium chrysogenum*, **9,** 125
Laricresinols, from *Picea excelsa*, configuration **L20,** 1
LCAO treatment, acidity of hydrocarbons, **L6,** 23
α-**Lecithin** "mixed acid" synthesis, **L9,** 1
L-α-**Lecithins,** "mixed acid," partial synthesis, **L22,** 7
Lecithins, synthetic, synthesis, **L9,** 1
Lespieau reaction, synthesis of heterocyclic diacetylenes, **L26,** 25
Lewis acid—nitro compd. system, strong electron acceptor, **L9,** 5
Lichen acid, siphulin, chromanone type, proposed structure, **L4,** 1
Lignans, of *Picea excelsa*, **L20,** 1
Linoleic acid, alkali fusion, **8,** 239
Lithium organic reagents, reaction with perfluorovinyl derivatives of tin and silicon, **L22,** 20
reaction with dichlorodiphenylsilane, formation of dodecaphenylcyclohexasilane, **L23,** 5
solution in amines, reduction of aromatic hydrocarbons to mono-olefins, **L16,** 1
Lithium hexaphenyl antimonide, dissociation, **10,** 37
Lithium piperidide, action in benzyne formation from fluorobenzene, **9,** 29
and phenyllithium, efficiency in formation of arynes, **9,** 29
Longiborneol, identical with juniperol, macrocarpol and kuromatsuol, **9,** 237
Longicamphor, 8, 43
Longifolene, hydration, **8,** 42
identical with junipene and kuramatsuene, **9,** 237
NMR, **9,** 1
Lumisterol, provitamin D, previtamin D and tachysterol, photochemical interconversions, **11,** 276
Lunarine, degradation, isolation of spermadine, **L18,** 36
Lycodine, structure, **L20,** 9
Lycopodium alkaloids, biogenesis, **L10,** 34
structure, stereochemistry and interrelationship, **L20,** 13
Lycorenine, lycorine, caranine and pluviine, configurational relationship, **11,** 89
Lycorine, caranine, pluviine and lycorenine, configurational relationship, **11,** 89
Lycotonine, chemistry, **9,** 284
Lysolecithins, acylation to "mixed acid" α-lecithins, **L9,** 1
γ-**Lysolecithins,** acylation to "mixed acid" lecithins, **L22,** 7

Macrocarpol, identical with juniperol, kuromatsuol and longiborneol, **9,** 237
Maleic acid, photodimerization to cyclobutane derivatives, **L3,** 13

Maleic anhydride, addition to benzene and aromatic compds., **L21,** 1
Manoyloxide, stereochemistry, **10,** 71
Mass law effect, in solvolysis of *p*-chlorobenzhydrylchloride, **L22,** 12
Mass Spectrometry, detn. of sarpagine carbon skeleton, **L15,** 9
Mechanism, autoxidation of cumene, O^{18}tracer evidence, **L24,** 30
bromination and mercuration in isoquinoline, **8,** 23
chromic acid oxidation of diphenylmethane, **8,** 330
formation of camphor from homocamphoric acid, **L2,** 19
hydride transfer reactions, **L21,** 20
isotope exchange reactions of dialkylmercury and alkylmercuric halides, **L19,** 7
organic reactions in strong alkalis, **8,** 221, 239, 246
polymerization of ethylene with Ziegler-Natta catalysts, **L17,** 12
thiocyanate and isothiocyanate isomerization, **L11,** 27
warfarin formation from 4-hydroxycoumarin and β-anilinobenzylacetone, **L13,** 23
Wittig reaction, **9,** 130
Melia azadirachta, constituents, **10,** 45
nimbin structure investigation, **11,** 67
DL-**Menthone,** bromination, **11,** 219
Mercuration, of isoquinoline, new mechanism, **8,** 23
Mercuric compds, organic, unsymmetrical, reaction with free radicals, **L3,** 25
Mercuridesilation, application, electrical effects of alkyl groups on an aromatic ring, **L15,** 1
Mercury compds., mechanism of isotope exchange reactions of dialkylmercury and alkylmercuric halides, **L19,** 7
Mesquitic acid acetate, reduction, **L7,** 20
Metagenin, structure, **L3,** 1
Metallocene reactions, role of metal atom, **L13,** 1
Metallorganic compds., cyclopentadienyltrimethyltitanium prep., **L14,** 19
4,7-**Methanoinden**-8-**one,** 4,5,6,7-tetrachloro-3a,4,7,7a-tetrahydro-, isomerization, **L11,** 5
Methyl diazoacetate, reaction with *cis*- and *trans*-butene, **10,** 65
Methyl group, intermolecular exchange, trimethylaluminium in cyclopentane, **L27,** 25
Methyl transfer, in biosynthesis of novobiocin and actinomyocin, **L25,** 26
2-Methylalanine, peptide synthesis from, **11,** 39
Methylation, transannular, of 2-amino-4-hydroxypteridine, **L25,** 17
1(3)-**Methylazulenes,** hydride hyperconjugation, **L27,** 1
2-Methylbutane, 1-chloro-, (−)-*trans*-1,2-dimethylcyclopropane from, **11,** 272
Methylcarbazoles, 2- and 4-trifluoro-, synthesis, **8,** 73, 79
Methylcyclohexane, reaction with Co, **10,** 55
2-Methylcyclohexanone, prep., **10,** 55
Methylcyclopentane, reaction with Co, **10,** 55
Methylcyclopropane, from isobutyl chloride, **11,** 266
Methylene, addition to butyne-2, **10,** 65
Methylenecycloheptatriene, *see* Heptafulvene.
Methylenecyclohexadienones, *see* Quinone methides,
Mevalolactone, fluorine derivatives, **L8,** 20
Michael reaction, reactivity of Schiff base intermediates, **L13,** 23
Mirene, conversion to isophyllocladene, **L24,** 18
structure, **11,** 226; **L24,** 18
Miropinic acid, identification, **8,** 356
MO-CCAO, semi-empirical, application to indoxazene and anthranil, **10,** 81
Molecular deformation, in cycloöctadecanonaene, **11,** 125
Molecular orbital calculations, non-classical aromatics, **11,** 121
Molecular orbital treatment, of isoquinoline, **8,** 23
Molecular structural analysis, as a means of determining interaction energy of nonbonded atoms, **9,** 183
Molecular structure, and estrogenic activity of substituted ethylenes, **8,** 205
Molecules, excited states, hyperconjugation in, **L2,** 1
organic, electronic spectra and interpretation, **10,** 102, 109, 118
Monascorubrin, proposed structure, **L5,** 24
Morphine, tyrosine incorporation, rate study, **L27,** 21
Myristic acid, from linoleic and stearolic acids, **8,** 239
Myrtanol, formation from β-pinene, **L21,** 9

Naphthalene, 1,6-dibromo-2,7-dimethoxy-, oxidation, **11,** 256
Naphthalene-2,7-**diol,** 1,6-dibromo-, transbromination, **11,** 256
structures of mono- and di-bromination products, **11,** 256
1,4-**Naphthaquinone**-6-**carboxylic acid,** 3-hydroxy-2-methyl-, structure for oosporein, **10,** 148
Naphthaquinones, derivatives of naphthalene-2,7-diol, **11,** 256
Naphthol AS-KN, constitution, **11,** 143
Naphthol AS-RS, constitution, **11,** 143
Naphthol [2,3-a] **pyrene,** homologues, synthesis, **8,** 1
1,2-**Naphthyne,** formation, **9,** 29
Neoline, structure, **L3,** 17
Neoquassin, structure, **L20,** 25
Neoruscogenin, structure, **L19,** 25
Nepetalinic acids, stereochemistry, **L11,** 18
Nimbin, structure investigation, **11,** 67
Nimbiol, from podocarpic acid, **L9,** 20
structure, **10,** 45; **11,** 22
Nimbiol methyl ether, synthesis, **L9,** 16
Nimbosterol, identical with β-sitosterol, **10,** 45

Nitro comp.—Lewis acid system, strong electron acceptor, **L9,** 5
Nitro groups, terminal, effect on electronic spectra of conjugated hydrocarbon systems, **10,** 109
Nitroanthraquinones, halogen compds., nucleophilic reactions, **8,** 107
Nitrobenzene, bond lengths, **8,** 13
ionization and dissociation of triphenylchloromethane in, **L18,** 10
Nitrogen and Co, hybridization of *s* and $p\sigma$ orbitals, interpretation of chemical properties, **10,** 212
Nitromethane—aluminium chloride system, electron attractions by, **L9,** 5
Nitrones, 1.3-dipolar addition, **L12,** 9
Nomenclature, flavonoid, **8,** 336
steroid, **8,** 360
β-Nor-6-aza-6-methylequilenin, attempted synthesis, **10,** 230
A-Nor-5α-cholestan-1-one, synthesis, **1,** 199
A-Nor-5α-cholestanes, stereochemistry, **11,** 199
DL-B-Nor-6-oxaequilenin, synthesis, **10,** 223
18-Norsteroids, DL-18-nortestosterone synthesis, **L8,** 11
DL-18-Nortestosterone, synthesis, **L8,** 11
19-Nortestosterone, 2-hydroxyestradiol synthesis from, **10,** 144
Novobiocin, biosynthesis, C-methylation example, **L25,** 26
Nucleophilic localization energy, isoquinoline, **8,** 23
Nucleophilic reactions, attack on isoquinoline, **8,** 29
of halonitroanthraquinones, **8,** 107
stereochemistry of thiophenol addition to propiolic acid and ethyl propiolate, **L4,** 18
Nucleophilic reagents, reaction with 2-fluoroethanol, **10,** 160
reactivity with 2-aryl-4-methyl-4-chlorocarbonyloxymethyl-2-oxazolines, **9,** 175
Nucleophilicity in bimolecular nucleophilic substitution, **L9,** 24

Obacunone, chemical constitution, **L8,** 1
β-Obscurine, relationship to lycodine, **L20,** 9
α- and β- Obscurine, structures, **L10,** 19
Octadecanoic acid, alkali fusion, **8,** 227
9, 10-dihydroxy-, alkali fusion, **9,** 247
10- and 12-hydroxy-, dehydrogenation, **8,** 253
10-oxo-and hydroxy-, alkali fusion, **8,** 249
12-oxo- and hydroxy-, alkali fusion, **8,** 247
9,10,12-trihydroxy-, alkali fusion, **9,** 250
Octafluorocyclohexa-1:4-diene, reaction with oleum, **8,** 38
Octahydroanthracene, symmetrical, prep., **8,** 1
Octahydrodimethanonaphthyl ion, non-classical homocyclopropenyl cation formation, **L25,** 4
1,2,3,4,4a,5,6,7-Octahydronaphthoic acid, 7-ketomethyl ester, prep., **8,** 163
Octahydrophenanthrene, condensation with terephthalyl chloride, **9,** 96
α-Octyl-α-hydroxysebacic acid, prep. and benzilic rearrangement, **9,** 246
Olefinic unsaturation, detn. in mono- and polysulphides, **9,** 58
Olefins, diacylation, prep. of pyrylium salts, **L2,** 7
mono-, by reduction of aromatic hydrocarbons **L16,** 1
proportions in E_2 eliminations, effect of leaving group, **L18,** 1
steriod, *cis*-addition of fluorine, **L20,** 34
α-Olefins, polymerization, **8,** 86
Oleic acid, alkali fusion, **8,** 224
Oligopeptides, open chain, synthesis, **11,** 39
Oligosaccharides, of amino sugars, synthesis, **9,** 116
Olivacine, structure, **L1,** 18
Oosporein, degradation to tomichaedin, **10,** 148
Optically active compds., steric correlations by quasi-racemate method, **8,** 126
Organolithium reagents, reaction with perfluorovinyl derivatives of tin and silicon, **L22,** 20
Organometallic alkenyl compds., geometrical isomers of stibinous and stibinic propenyls **L8,** 23
Orgels parameters, use in MO-LCAO calculations, **10,** 81
1,3,4-Oxadiazoles, 2,5-disubstituted, synthesis, **11,** 241
synthesis, **11,** 241
2-Oxazolines, 2-aryl-4-methyl-4-chlorocarbonyloxymethyl-, chemical reactivity and I.R. Spectra, **9,** 175
Oxidation, auto-, of cumene, mechanism, **L24,** 30
catalytic, of primary and secondary alcohols, **9,** 67
chromic acid, of diphenylmethane, kinetics, **8,** 331
hydrogen-abstraction theory, **8,** 350
$KmnO_4$, of aromatic trifluoromethyl alcohols, deuterium isotope effect, **L2,** 28
organic sulphides with optically active peroxy acids, **L6,** 20
perbenzoic acid, isomeric *p*-dimethylaminophenylazopyridines, **9,** 194
processes, mechanisms, **8,** 350
steroidal allylic alcohols to αβ-unsaturated ketones, **L9,** 14
Oximation, of *o*-alkylbenzophenone, **9,** 210
Oxodicyclopentadienes, rearrangements, **L22,** 29
9-Oxoheptadecanoic acid, prep., **9,** 246
13-Oxopodocarpane, 8β-carbomethoxy-, stereospecific total synthesis, **L17,** 1
8β-carboxy, from isophyllocladene, **8,** 261
13-Oxopodocarp-8(14)-ene, from isophyllocladene **8,** 261
Ozonation, polycyclic aromatics, effect of solvent, **L13,** 14
Ozone, reaction with organic hydroperoxides, **L14,** 1
Ozonides, solvolysis, **L26,** 30

Papilionaceae, alkaloids, **11,** 78

Pectic acid acetate, reduction, **L7,** 22
Penicillium chrysogenum, action on lactose, **9,** 125
Pent-2-ene, *cis* or *trans*-2-methyl-2(6′-methoxy-2′-naphthyl)- prep., **8,** 150
Pent-3-enoic acid, 2-methyl-3-(6′-methoxy-2′-naphthyl)-*cis* or *trans* ethyl ester, prep., **8,** 150
Pentacenes, synthesis, **L1,** 5
Pentamethincyanines, trinuclear, dyes, **9,** 106
Pentanoic acids, *threo-* or *erythro-* 2-methyl-3-(6′-methoxy-2′-naphthyl)-, prep., **8,** 150
Pentaphenyl antimony, by dissociation of lithium hexaphenyl antimonide, **10,** 37
Peptides, amino-oxy, DL-canaline derivatives, **L18,** 28
from 2-methyl-alanine, **11,** 39
of amino alkyl sulphonic acids, synthesis, **9,**289
synthesis, **L14,** 9
Peracids, formation by acidolysis of ozonides, **L26,** 34
Perchlorostilbenes, *cis-* and *trans-*, thermal stereomutation, **9,** 156
Peropyrene, benzologues and other derivatives, **10,** 26
Peroxy acids, optically active, oxidation of organic sulphides, **L6,** 20
Peroxycompounds, copper salt catalysed reactions of t-butyl perbenzoate with benzyl ethers, **L2,** 4
Petroselenic acid, alkali fusion, **8,** 226
Phaseolus multiflorus, isolation of gibberellins A_1 and A_5, **11,** 60
Phenanthro [2,3-a] **pyrene,** formylation, **8,** 7
9,10-**Phenanthryne,** formation, **9,** 29
6β-**Phenoxypregnan**-3β,5α-**diol**-20-**one**-3 acetate, prep. and conversion to 6α-phenoxyprogesterone, **8,** 116
6α-**Phenoxyprogesterone,** prep., **8,** 116
Phenyl groups, effect on absorption spectra of pyrilium salts, **9,** 167
Phenylalkyl series, direct nucleophic substitution, **L12,** 18
Phenylation, of dimedone, di- and tri-benzoylmethane, **8,** 49
Phenylazopyridines, isomeric *p*-dimethyl-, amino oxidation, **9,** 194
Phenylcarbene, from benzyl chloride and N-butyllithium, **L24,** 26
4-**Phenylcyclohepta**-1,3-**dione,** prep. and prop., **11,** 154
2-**Phenylcyclopentanone,** 2-acetyl-, prep. and prop., **11,** 154
Phenyllithium and lithium piperidide, efficiency in formation of arynes, **9,** 29
by dissociation of lithium hexaphenyl antimonide, **10,** 37
Phenylpyrazoles, substituted, formation from 2-diazoacetophenone, **L17,** 22
5-**Phenyltetrazole,** condensation with *p*-cyanobenzoyl chloride, **11,** 241
Phenyltrifluoromethyl carbinols, $KMnO_4$ oxidation, deuterium isotope effect, **L2,** 28
Phosphonium fluorenylide, trimethyl- and tri-n-butyl, prep., **9,** 130
Phosphorus compds., organic, application of Hammett equation, **9,** 15
Phosphorus thio-acids, acidity and structure, **9,** 10
synthetic methods and ionization constants, **9,** 17
Photochemical reactions, bicyclo [2.2.0]-hexane synthesis, **L21,** 24
cyclization of azobenzene, **L9,** 12
interconversions, of provitamin D, previtamin D, tachystero and lumisterol, **11,** 276
of 20-ketosteroids, **L4,** 10
maleic anhydride addition to benzene and other aromatic compds., **L21,** 1
reduction of CO_2, **L18,** 22
Photochlorination, of perchlorostilbenes, **9,** 156
Photodimerization, of maleic and fumaric acid derivatives, **L3,** 13
of N-methyl-2 piperidone, **L25,** 1
of α,β-unsaturated lactams, **L25,** 1
Photolysis, of aromatic disulphides, **10,** 76
Phyllocladene, degradation product, total synthesis, **L18,** 24
isomerization to isophyllocladene and reaction with Prevost reagent, **L17,** 9
ketones from, **11,** 226
stereospecific total synthesis of DL-8β-carbomethoxy-13-oxo-podocarpane, **L17,** 1
Picea excelsa, lignans, **L20,** 1
Picrotoxinin, molecular structure and absolute configuration, **L19,** 21
Pigments, fungus, **10,** 135
spinochrome E structure, **L1,** 11
DL-**Pimaradiene,** synthesis, **L25,** 37
Pimaric acids, ring C substitution pattern, **L25,** 37
β-**Pinene,** hydroboration, **L21,** 9
Pinoresinols, absolute configuration, **L20,** 3
from *Picea excelsa*, configuration, **L20,** 1
Piperidones, conformation of 4-hydroxy compds., **L14,** 23
Pithecolobine, structure, **L16,** 11
Plants, higher, ureide biosynthesis, **L25,** 32
Pluviine, lycorine, caranine and lycorenine, configurational relationship, **11,** 89
Podocarpaceae, chemistry, part V, **8,** 356
(±)-5,7,13(14)-**Podocarpatriene,** 6-methoxy-7-methyl-, synthesis, **L9,** 16
Podocarpic acid, conversion to nimbiol, **11,** 22; **L9,** 20
Podocarpus ferrugineus, miropinic and isomiropinic acids from, **8,** 356
Polyalkylbenzenes, aromatic halogenation, reaction selectivity, hydrogen isotope effect and steric hindrance, **L23,** 30
Polyaryls, synthesis, with alternating phenyl and 1,3,4-oxadiazole rings, **11,** 241
Polycyclic compds., aromatic, ozonation, effect of solvent, **L13,** 14
Polyene, cyclic, $C_{18}H_{18}$, molecular deformation, **11,** 125
Polyfluorocyclohex-anes, -enes and **dienes,** defluorination, **9,** 240

Polyhatomethanes, reaction with enolethers of A^4-3-ketosteroids, **9,** 149
Polymerizations, co-ordinated, anionic, **8,** 96
ionic, stereospecificity, **8,** 99
ethylene, reaction mechanism with Ziegler-Natta catalysts, **L17,** 12
HCN tetramer, structure, **L6,** 17
ionic, organometallic complexes as catalysts, **8,** 86
Polypropylene, isotactic, formation with Ziegler-Natta catalysts, **L17,** 17
Porphyrin, NMR resonance spectra, **L2,** 23
Porphyrin *a*, position of formyl group, **8,** 266
5,16-**Pregnadiene-20-one,** 3β-acetoxy-12β-hydroxy-12α-methoxy-, prep., **10,** 238
5,16-**Pregnadiene**-12,20-**dione,** 3β-acetoxy-, prep. from gentrogenin, **10,** 238
Pregnane derivatives, total synthesis, **L17,** 27
5α-**Pregn**-16-**en-2-one,** 3β-acetoxy-, synthesis of solanum alkaloids, **L27,** 5
5α,16-**Pregnene**-12,20-**dione,** 3β-acetoxy-, prep. from hecogenin, **10,** 238
5α,16-**Pregnene**-20-**one,** 3β-acetoxy-12β-hydroxy-12α-methoxy-, prep., **10,** 238
Δ^{16}**Pregnenes,** 16-methyl, formation from of 16α-methyl-17α-hydroxy pregnane, **8,** 217
Pregnenolone acetate-α**-epoxide,** fission with boron trifluoride etherate, **8,** 116
Previtamin D, provitamin D, lumisterol and tachysterol, photochemical interconversions, **11,** 276
Prevost reaction, action of silver iodobenzoate on isophyllocladene, **L17,** 9
Progesterones, 16-methylene, synthesis, **L16,** 21
Propenyl compds., stibinous and stibinic, geometrical isomers, **L8,** 23
Propiolic acid, and ethyl ester, stereochemistry of nucleophilic addition of thiophenols, **L4,** 18
Propionic acid, 2(2′-hydroxy-4′-methylcyclohex-1′-yl)-synthesis of stereoisomeric lactones, **9,** 295
L-**Propionic acid,** α-amino-β-(pyrazoyl-N)-, synthesis, **11,** 231
3-**Propionic**-2,4,5-**pyrroletricarboxylic acid,** by degradation of porphyrins, **8,** 266
Protonation, of indoles, position, **L21,** 12
Provitamin D, lumisterol, previtamin D and tachysterol, photochemical interconversions, **11,** 276
Pschorr reaction, prep. of carbazoles, **8,** 79
Pteridine, 2-amino-4-hydroxy-, transannular methylation, **L25,** 17
2-**Pyridone,** N-methyl-, photodimerization, **L25,** 1
Pyrylium salts, alkyl- and phenyl-, absorption spectra, **9,** 163
prep. by olefin diacylation, **L2,** 7
Pyrromycinone, identity with rutilantinone, **L8,** 25
position of carbomethoxy group, **L8,** 25

Quabagenin, from 1α,11α-epoxy-steroids by transannular substitution, **L27,** 31
Quasi-racemate method, steric correlations of optically active compds., **8,** 126
Quassin, structure, **L20,** 25
Quinolines, hydrogenated, analgesics, **8,** 296, 304; **10,** 175
Quinone methides, prep. and behaviour, **L25,** 9

R-bands, thiobenzophenone, effect of substituents, **10,** 123
Racemization, in solvolysis of *p*-chlorobenzhydryl chloride, **L22,** 12
rate, of *p*-chlorobenzhydryl chloride in acetone, **L2,** 31
Radiation, ^{60}Co-γ-, reduction of CO_2, **L18,** 17
Radical localization energy, of isoquinoline, **8,** 23
Radicals, free, and unsymmetrical organomercuric compds., reactions, **L3,** 25
effect of copper salts, **L2,** 4
Radioactive chloride exchange of *p*-chlorobenzhydryl chloride in acetone, **L2,** 31
Radioactive diacyl compds., reaction of isocyanates and acid anhydrides with ^{14}C, **L2,** 15
Reduction, ^{60}Co-γ-radiation, CO_2 in aqueous solution, **L18,** 17
diborane, of carboxyl groups in carbohydrates, **L7,** 17
selective, by lithium-amine systems, **L16,** 1
metallic, of camphor to isoborneol, **L21,** 16
Resonance, and conjugation, **11,** 96
and polar effects, separation in reaction of chlorine atoms, **8,** 101
energy, of dibenzodiphenylene and *cis*-isomer, **10,** 41
in arylazopyridine systems, **9,** 194
in benzene derivatives, **8,** 13
steric enhancement, **L25,** 21
steric inhibition, to thermal stereomutation of *cis*- and *trans*- perchlorostilbenes, **9,** 156
substituent and solvent effects on $n \rightarrow \pi(^1U \leftarrow {}^1A)$ transition in aliphatic carbonyl derivatives, **L2,** 1
Retamine, chemistry and stereochemistry, **11,** 78
Rhodanines, substituted, N-glucosyl derivatives, **L6,** 10
Ricinoleic acid, fission in strong alkali, **8,** 246
Rimuene, structure observations, **L25,** 37
Royal jelly acid, synthesis, **L4,** 15
Rutilantinone, identity with pyrromycinone, **L8,** 25
Ryanodine, skeletal structure, **L15,** 31

Samogenin from metagenin, **L3,** 1
DL-**Sandaracopimaradiene,** synthesis, **L25,** 37
Santonin, configuration, **8,** 193
Sapogenins, kogagenin, structure, **10,** 1
metagenin structure, **L3,** 1
12-methyl hemiketals from 12-keto-16-dehydropregnenes, **10,** 238
neoruscogenin, structure, **L19,** 25
nomenclature, **8,** 360

Sarpagine, carbon skeleton, detn. by mass spectrometry, **L15,** 9
Saussurea lappa, sesquiterpene lactone, costunolide structure, **9,** 275
Schiff bases, reactivity as intermediates in Michael reaction, **L13,** 23
Schmidt reaction, between hydrogen azide and ketones, mechanism, **9,** 210
Schöpf-oechler scheme for vasicine synthesis, **L25,** 44
Selagine, structure, **L10,** 26
proof, **L12,** 14
Selinane, *see* Eudesmane
Sesamins, absolute configuration, **L20,** 3
Sesquiterpenes, (±)-cadinene dihydrochloride synthesis, **L27,** 27
carotol structure, **8,** 271
costunolide structure, **9,** 275
eudesmane, stereochemistry, **8,** 181
from cupressales, **9,** 237
proton magnetic resonance spectra, **9,** 1
studies—XVI, **8,** 171
studies—XVII, **8,** 42
valeranone constitution, **L7,** 9
Silicon, perfluorovinyl derivatives, reaction with organolithium reagents, **L22,** 20
Siphulin, lichen acid, chromanone type, proposed structure, **L4,** 1
β-Sitosterol, identical with nimbosterol, **10,** 45
Skatole, basicity relative to 2-methylindole, **L21,** 14
dimer, structure, **L26,** 13
Sodium, reaction with dichlorodiphenylsilane, formation of dedecaphenylcyclohexasilane, **L23,** 5
Solanocapsin, absolute configuration at C-25, **L27,** 9
Solanum alkaloids, synthesis from 3β-acetoxy-5α-pregn-16-en-20 one, **L27,** 5
Solvents, effects, reactions of free radicals and atoms, **8,** 101
isomer distribution in chlorination of aromatics, **L13,** 9
ozonation of polycyclic aromatics, **L13,** 14
$n \rightarrow \pi(^1U \leftarrow {}^1A)$ transition in aliphatic carbonyl derivatives, **L2,** 1
isotope effect, D_2O and H_2O, **10,** 182
H_2O—D_2O mixtures, **10,** 200
kinetics of bimolecular substitution by anionic bases in alcohol–water mixtures, **L24,** 1
Solvolysis, of γ-aminopropyl chlorides, **L23,** 25
of *p*-chlorobenzhydryl chloride, ion pairs, racemization, chloride exchange and mass law effect, **L22,** 12
of cyclopropylcarbinyl chloride, **11,** 171
of ozonides, **L26,** 30
Sophorol, structure, **L19,** 16
Sparteine, 8-hydroxy-, retamine and isoretamine epimers, **11,** 78
(+)-Sparteine, 8-chloro-, chlororetamine structure, **11,** 78
Spectra, absorption, 4-aminoazobenzene and derivatives, **10,** 130
alkyl- and phenyl-substituted pyrylium salts, **9,** 163
isomeric *p*-dimethylamino-phenylazo-pyridines, **9,** 194
molecular complexes, **10,** 96
charge resonance, substituent effects in 1,1-dinitroalkane anions, **L27,** 17
electronic, conjugated hydrocarbon systems, effect of terminal NO_2 and NH_2 groups, **10,** 109
organic molecules and their interpretation, **10,** 102, 109, 118
p-terphenyl and derivatives, **10,** 102
thiobenzophenone and derivatives, interpretation, **10,** 118
I.R., 1-amidine-3-aryleneas, **10,** 15
2-aryl-4-methyl-4-chlorocarbonyl-oxymethyl-2-oxazolines, **9,** 175
cadinene dihydrochloride, **L27,** 29
carotol, **8,** 271
costunolide, **9,** 277
cyclobutadiene silver nitrate, **L26,** 35
fluorene derivatives, **11,** 252
humulene, **9,** 8
intensity measurements on diazocompounds, **11,** 285
ionic solutions, **10,** 188
3-methoxy-10-oxo-8-aza-des-N-morphinan, **10,** 175
12-methyl hemiketals, **10,** 238
N-methyl-8-aza-des-N-morphinan, **8,** 299, 307
quassin and neoquassin, **L20,** 25
thelephoric acid, **10,** 135
verbenalin, **L26,** 7
zerumbone, **8,** 175
NMR, of C-dihydrotoxiferine, **L26,** 3
18,20-cyclasteroids, **L4,** 13
cyclopenta[c]thiapyran, 5,7-dichloro- and 5,7-dithiocyanocyclopenta[c]thiapyran, **L2,** 13
humulone, **9,** 272
indoles, **L21,** 12
longifolene, zerumbone, humulene and their hydroderivatives, **9,** 1
porphyrin, **L2,** 23
quassin and neoquassin, **L20,** 25
ring A structure of cucurbitacin B, **L15,** 15
ruscogenin and neoruscogenin, **L19,** 25
sesquiterpenes, **9,** 1
trimethylaluminium in dimethylcadmium, **L27,** 25
U.V., and estrogenic activity in substituted ethylenes, **8,** 205
2,5-disubstituted 1,3,4-oxadiazoles, **11,** 241
ergosterol, **11,** 281
heptafulvene, **11,** 188
indoles, **L21,** 12
lumisterol, tachysterol and ergosterol, **11,** 281
12-methyl hemiketals, **10,** 238

Spectra, U. V. (*continued*)
N-methyl-2-pyridone dimer, **L25,** 1
quassin and neoquassin, **L20,** 25
quinone methides, **L25,** 13
Spermidine, by degradation of lunarine, **L18,** 36
Spinochrome E, hexahydroxynaphthaquinone structure, **L1,** 11
25D-**Spirostane**-1β, 2β, 3α, 5β-**tetrol,** kogagenin structure, **10,** 1
25D,5β-**Spirostane**-2β,3β,11α-**triol,** metagenin structure, **L3,** 1
Stearolic acid, alkali fusion, **8,** 239
Stereochemistry, A-substituted A-nor-5α-cholestanes, **11,** 199
absolute configuration of thelepogine methiodide, **L26,** 18
cis-trans isomerism of steroidal $\Delta^{17(20)}$ enol acetates, **8,** 145
configuration of (+)-3-methyl-3-t-butyl-1-chloroallene, **L8,** 16
conformational analysis of alicyclic compds., **9,** 40
cucurbitacins, **L22,** 23
dehydroabietic acid, synthesis of 2 stereoisomers, **L23,** 1
2,4-dibromomenthone, **11,** 219
erythrinan alkaloids, **L14,** 5
eudesmane sesquiterpenes, **8,** 181
geometrical isomers of stibinous and stibinic propenyl compds., **L8,** 23
guaiol, **L22,** 33
guaiol, hepetalinic acids and iridomyrmecins, **L11,** 18
jacobine bromhydrin, **L23,** 35
lycodine and β-obscurine, **L20,** 9
lycopodium alkaloids, **L20,** 13
manoyl oxide, **10,** 71
N-methyl-8-aza-des-N-morphinan, **8,** 304
nucleophilic addition of thiophenols to propiolic acid and ethyl propiolate, **L4,** 18
quasi-racemate method, **8,** 126
relations between lycorine, caranine, pluviine and lycorenine, **11,** 89
retamine, **11,** 78
role of metal atom in metallocene reactions, **L13,** 3
sapogenins and alkaloids, **8,** 360
sesamins and pinoresinols, absolute configuration, **L20,** 3
solanocapsin, absolute configuration at C-25, **L27,** 9
total synthesis of DL-8β-carbomethoxy-13-oxopodocarpane, **L17,** 1
verbenalin, **L26,** 10
Stereoselective synthesis, of estrone, **L5,** 20
Steric enhancement, of resonance, **L25,** 21
Steric hindrance, in aromatic halogenation of polyalkylbenzenes, **L23,** 30
in thermal and catalysed isomerizations of chlorinated α,α'-dichlorostilbenes, **9,** 156
Steroids, Δ^5-3β-alcohol, *cis*-addition of fluorine, **L20,** 34
Steroids (*continued*)
allylic alcohols, oxidation to $\alpha\beta$-unsaturated ketones, **L9,** 14
contraction of 6- to 5-membered rings, **11,** 199
$\Delta^{17(20)}$ enol acetates, *cis-trans* isomerism, **8,** 145
5,6-epoxides, fission reactions induced by boron trifluoride etherate, **8,** 116
16α,17α-epoxides, ring opening, **L17,** 34
1α,11α-epoxy-, transannular substitution to quabagenin, **L27,** 31
gem-methoxy hydroperoxy, formation, **9,** 145
heterocyclic, synthesis, **10,** 215, 223, 230
19-hydroxy-10-isotestosterone synthesis, **L22,** 38
17-hydroxy-20-keto, D-homoannulation, **11,** 163
16α-methyl-17α-hydroxy, formation, **8,** 217
16-methylene, synthesis, **L16,** 21
6α-methylsteroids, synthesis and biological activity, **9,** 149
nomenclature, **8,** 360
ring A formation, **8,** 163
total synthesis of pregnane and androstane derivatives, **L17,** 27
Stilbene, *p*-nitro *p'*-amino derivatives, electronic spectra and interpretation, **10,** 109
Stilbenes, thermal and catalysed isomerizations, **9,** 156
Stobbe reaction, of benzyl ketones, **11,** 158
Strichnine bases, biogenetic laboratory synthesis, **L19,** 30
Structure, effect on *cis-trans* equilibrium of α-hydrindanones, **L18,** 4
Substituents, effects, in aromatic substitution, **L15,** 1
in charge-resonance spectra of 1,1-dinitroalkane anions, **L27,** 17
of OMe, OH, NMe_2 and charged O^- atom on K- and R-bands of thiobenzophenone, **10,** 118
on $n \rightarrow \pi('U \rightarrow 'A)$ transition in aliphatic carbonyl derivatives, **L2,** 1
on R- and K- bands of thiobenzophenone, **10,** 123
para, effect on K-bands of a *p*-polyphenyl series, **10,** 102
terminal NO_2 and NH_2 groups, effect on K-bands of conjugated hydrocarbon systems, **10,** 109
Substitution, bimolecular, by anionic bases in alcohol-water mixtures, interpretation of kinetics, **L24,** 1
direct nucleophilic, in hydrocarbon chains, transition of polar effects, **L12,** 18
electrophilic, mechanism for isoquinoline, **8,** 23
nucleophilic bimolecular, ion pairs, nucleophilicity and salt effects, **L9,** 24
transannular, quabagenin from 1α,11α-epoxy steroids, **L27,** 31
Sugiol, identity of isomiropinic acid, **8,** 356
Sulphides, organic, oxidation with optically active peroxy acids, **L6,** 20

Sulphonic acids, isomeric, of 2,6-di-t-butylpyridine, syntheses and structure, **L1,** 13
Sulphoxides, asymmetrical synthesis, **L6,** 20
Sulphur compds., acetoacetic acid-dithioketals prep., **L11,** 1
condensed thiophenes, synthesis, **9,** 76
involving free-radical reactions, **10,** 76
organic monosulphides, reaction with 2,4-dinitrobenzenesulphenyl chloride, **9,** 58

Tautomerism, equilibrium, application of Hammett equation, **9,** 10
mono-acid cations of 4-aminoazobenzene and derivatives, **10,** 129
Tectorigenin, synthesis, **L5,** 6
Tellurium trihalides, aryl, prep., **11,** 15
Terephthalonitrite, synthesis of 9 ring polyarlys from, **11,** 241
Terephthalyl chloride, condensation with octahydrophenanthrene, **9,** 96
Terminalia tomentosa, new triterpene carboxylic acid from, **L27,** 12
Terpenes, steric relations, quasi-racemate method, **8,** 137
Terpenoids, and related compds., **10,** 45
nimbin structure investigation, **11,** 67
part XXI, **9,** 275
p-**Terphenyl** and derivatives, electronic spectra and interpretation, **10,** 102
5,6:8,9:14,15:17,18-**Tetrabenzoheptacene,** synthesis, **9,** 96
Tetracyclines, synthesis of related substances, **11,** 52
2,3,8,9-**Tetrahydroxybenzobis**[1,2-b,4,5-b′]**benzofuran**-6,12-**quinone,** structure of thelephoric acid, **10,** 135
Tetrahydrocannabinol, separation from hashish components, **10,** 153
1,2,3,4-**Tetrahydrodibenzofuran,** synthesis of DL-β-nor-6-oxaequilenin from, **10,** 223
1,2,3,4-**Tetrahydrodibenzothiophene,** 3-cyano-7-methoxy-3-methyl-4-oxo- synthesis, **10,** 512
2,3,6,7-**Tetramethoxyphenanthrene**-9,10-**dicarboxylimide,** synthesis, **9,** 53
Tetrazoles, formation from α-diazoacetophenone, **L17,** 22
Thebaine, tyrosine incorporation, rate study, **L27,** 21
Thelephoric acid, structure, **L16,** 4
structure and synthesis, **10,** 135
Thelepogine methiodide, molecular structure and absolute configuration, **L26,** 18
Thiapyrans, condensed, synthesis, **9,** 76
Thiapyrylium cation, synthesis, **L23,** 11
Thiazole amino acids, synthesis, **L1,** 23
Thioanisoles, substituted, steric enhancement of resonance, **L25,** 21
Thiobenzophenone and derivatives, electronic spectra and interpretation, **10,** 118
Thiocyanates and isothiocyanates, equilibrium, kinetics and isomerization mechanism, **L11,** 27
Thione–Thiol equilibrium, **9,** 10
Thiophene isoesters, of polycyclic carcinogenic hydrocarbons, **9,** 76
Thiophenes, condensed, synthesis, **9,** 76; **L6,** 30
Thiophenols, stereochemistry of nucleophilic addition to propiolic acid and ethyl propiolate, **L4,** 18
Thiophenoxytellurine, prep., **11,** 15
Thiostrepton, amino acids, synthesis, **L1,** 23
Tin, perfluorovinyl derivatives, reaction with organolithium reagents, **L22,** 20
Titanium, organometallic complexes, synthesis, **8,** 86
Titanium compds., cyclopentadienyltrimethyltitanium prep., **L14,** 19
Toluene, chlorination, effect of solvent on isomer distribution, **L13,** 9
oxidation to benzyl chloride, mechanism, **8,** 350
p-**Toluenethiol,** addition to ethyl propiolate, **L4,** 18
Tomentosic acid, new triterpene acid from *Termentalia tomentosa,* **L27,** 12
Tomichaedin, from oosporein, **10,** 148
Transbromination, of 1,6-dibromonaphthalene-2,7-diol, **11,** 256
Transmethylation, in novobiocin and actinomycin biosyntheses, **L25,** 26
Trialkylphosphoniumfluorenylides, prep., **9,** 130
Trianisylethylene, structure and estrogenic activity, **8,** 205
Triazine ring fission, **11,** 133
1,3,5-**Triazine** derivatives, **11,** 133
Tribenzo[a,c,i]**naphtacene,** formylation, **8,** 7
Tribenzo[a,c,i]**pyrene,** synthesis, **8,** 1
Tribenzotetracene, synthesis, **10,** 171
Tribenzoylmethane, phenylation, **8,** 49
α,α,β-**Trichloroethyldimethylamine,** prep., **11,** 1
Tricyclic compds., prep. of 6,7-Benzocoumaran-2-ones, **11,** 158
Trifluoroacetate ethyl ester, condensation with diethyl succinate, **10,** 164
5,5,5-**Trifluorolaevulic** acid, prep., **10,** 164
Trifluoromethyl alcohols, aromatic, $KMnO_4$ oxidation, deuterium isotope effect, **L2,** 28
5,5,5-**Trifluoropent**-3-**enoic acid lactone,** 4-hydroxy-, prep. and reduction, **10,** 164
5.5,5-**Trifluoropenta**-1,3-**diene,** prep., **10,** 164
5,5,5-**Trifluoropentane**-1,4-**diol,** prep., **10,** 164
Trimethincyanines, trinuclear, dyes, **9,** 111
unsymmetrical, prep., **9,** 106
Trimethylaluminium in dimethylcadmium, intermolecular methyl exchange, **L27,** 25
Trimethylethylene, see Amylene.
2,4,6-**Trimethylpyrylium salts,** prep., **L2,** 7
4,5,6-**Triphenyl**-v-**triazine,** by 1-azido-1,2,3-triphenylcyclopropene rearrangement, **L13,** 19
1,2,3-**Triphenylcyclopropene,** 1-azido-, rearrangement to 4,5,6-triphenyl-v-triazine, **L13,** 19
Triphenylchloromethane derivatives, ionization and dissociation in nitrobenzene, **L18,** 10

Triphenylcyclopropenyl azide, rearrangement to triphenyltriazine, **L26,** 42
Triphenylethylenes, unsymmetrical, estrogenic activity, **8,** 205
Triphenylphosphin-alkenes, alkylation, ketone synthesis, **L4,** 7
Triphenylphosphin-carbomethoxymethylen,C-alkylation, synthesis of acids, **L4,** 5
Triptycen, prep., **10,** 37
Triterpenes, new carboxylic acid from *Terminalia tomentosa*, **L27,** 12
Tropylium ion, formation of cycloheptatriene, hydride transfer reactions, **L21,** 20
Tropilium salts, conversion to benzene, **8,** 33
Turbicoryn, glycoside from *Turbina corymbosa*, **L7,** 30
Tylophora asmatica, chemical examination, **9,** 53
Tylophorine, structure, **9,** 53
Tyrosine, rate incorporation into morphine, codeine and thebaine, **L27,** 21

U-alkaloid C, structure, **L1,** 18
Undec-10-enoic acid, alkali fusion, **8,** 228
Undec-10-ynoic acid, alkali fusion, **8,** 243
Unsaturation, olefinic, detn. in mono- and polysulphides, **9,** 58
Ureas, substituted, synthesis, **10,** 12
Ureide biosynthesis, in higher plants, **L25,** 32

Valence bond theory, as interpretation of asymmetric annulation effects, **9,** 202
Valeranone, constitution, **L7,** 9
identity with jatamensone, **L3,** 9
Varrentrapp reaction, **8,** 221, 239, 246
Vasicine, synthesis, realization of Schöpf-Oechler scheme, **L25,** 44
Verbenalin, structure, **L26,** 5
Vibration amplitude of deuterium, effect on substitution, **L6,** 13
Vitamin D, photochemical isomerizations, **11,** 276

Warfarin, formation from 4-hydroxycoumarin and β-anilinobenzylacetone, **L13,** 23
Water, D_2O and H_2O, interpretation of isotope effects in mixtures, **10,** 200
structure difference, **10,** 182
Wittig reaction, mechanism, **9,** 130

X-ray, analysis, jacobin bromhydrin, **L23,** 35
diffraction, absolute configuration of picrotoxinin, **L19,** 21
study, cevine configuration, **L7,** 24

Ylids, chemistry, **9,** 130

Zanthoxylum shetsa DC, alkaloids, **8,** 293
Zapotin, structure, **9,** 139
Zapotinin, structure, **9,** 139
Zerumbone, monocyclic sesquiterpene ketone, **8,** 171
NMR, **9,** 1
Ziegler-Natta catalysts, formation of polypropylene, **L17,** 17
reaction mechanism in ethylene polymerization, **L17,** 12
Zingiber zerumbet, isolation of sesquiterpene, **8,** 171
Zwitterion compds., azomethin-imines, **L12,** 1, 5
synthesis, **L12,** 1

AUTHOR AND TITLE INDEX

Ackmann R. G., **Linstead** P., **Wakefield** B. J. and **Weedon** B. C. L. Organic reactions in strong alkalis—I. Fission of ethylenic acids (the Varrentrapp reaction). **8,** 221

Ackmann R. G., **Dytham** R. A., **Wakefield** B. J., and **Weedon** B. C. L. Organic reactions in strong alkalis—II. Fission of di-ethylenic and acetylenic acids. **8,** 239

Adam G. See **Schreiber** K. **L27,** 5

Aghoramurthy K., **Sarma** K. G. and **Seshadri** T. R. The structure of thelephoric acid. **L16,** 4; **L23,** 38

Agnihotri R. K. See **Benkeser** R. A. **L16,** 1

Akiyoshi S., **Erdtman** H. and **Kubota** T. Chemistry of the natural order cupressales—XXVI. The identity of junipene, kuromatsuene and longijolene and of juniperol, kuromatsuol, macrocarpol and longiborneol. **9,** 237

Alderweireldt F. See **Shoolery** J. N. **9,** 271

Ali M. A. and **Coulson** C. A. On the stability of substituted diphenylenes. **10,** 41

Allred A. L. and **McCoy** C. R. Rapid intermolecular exchange of methyl groups. **L27,** 25

Anderson A. G., Jr., and **Harrison** W. F. Electrophilic substitution in cyclopenta[c]thiapyran **L2,** 11

Anet F. A. L. Structure, stereochemistry and interrelations of some *Lycopodium* alkaloids. **L20,** 13

Anet F. A. L. and **Rao** M. V. The structure of lycodine. **L20,** 9

Antoniades E. P. See **Smith** P. A. S. **9,** 210

Arnold Z. See **Zaoral** M. **L14,** 9

Arya V. P. see **Sommer** P. F. **L20,** 18

Axelrod L. R. see **Rao** P. N. **10,** 144

Ayer W. A. and **Iverach** G. G. The structures of α and β-obscurine. **L10,** 19

Babin D. R., **Findlay** J. A., **Forrest** T. P., **Fried** F., **Götz** M., **Valenta** Z. and **Wiesner** K. A contribution to the skeletal structure of ryanodine. **L15,** 31

Babin D. R. see **Wiesner** K. **9,** 254; **L3,** 17

Bachelor F. W., **Brown** R. F. C. and **Büchi** G. The constitution of ring A in aconitine. **L10,** 1

Baciocchi E., **Illuminati** G. and **Sleiter** G. Reaction selectivity, hydrogen isotope effect and steric hindrance in the aromatic halogenation of polyalkylbenzenes. **L23,** 30

Bacskai R. see **Trifan** D. S. **L13,** 1

Bader F. W. see **Swain** C. G. **10,** 182, 200

Bailey P. S. see **Dobinson** F. **L13,** 14

Baker W., **Downing** D. F., **Floyd** A. J., **Gilbert** B., **Ollis** W. D. and **Russell** R. C. Synthesis of irigenin and of tectorigenin, derivatives of 5,7-di-hydroxy-6-methoxyisoflavone. **L5,** 6

Balaban A. T. and **Nenitzescu** C. D. Preparation of pyrylium salts by olefin diacylation. The two pyrylium salts formed in amylene diacetylation with various catalysts. **L2,** 7

Balaban A. T. and **Nenitzescu** C. D. Reactions catalysed by aluminium chloride—XXVIII. The reaction of cycloalkanes with carbon monoxide. **10,** 55

Balaban A. T., **Sahini** V. E. and **Keplinger** E. Electronic absorption spectra of alkyl- and phenyl-substituted pyrylium salts. **9,** 163

Balasubramanian M. and **Padma** N. Conformation of some 4-hydroxypiperidines. **L14,** 23

Balasubramanian S. K. see **Banerjee** D. K. **L12,** 23

Balenovic K., **Bregant** N. and **Francetic** D. Oxidation of organic sulphides with optically active peroxy acids. Asymmetric synthesis of sulphoxides. **L6,** 20

Baliah V. and **Uma** M. Steric enhancement of resonance. **L25,** 21

Ballester M. and **Rosa** J. Steric hindrance in thermal and catalysed isomerizations of chlorinated α:α'-dichlorostilbenes **9,** 156

Ballio A. and **Russi** S. The structure of galactosyl-lactose, a trisaccharide produced from lactose by *Penicillium chrysogenum* Thom. **9,** 125

Balsillie A. see **Clar** E. **10,** 26

Banerjee D. K. and **Mahapatra** S. N. Synthesis of 1,3-dimethyl-1,3-dicarboxycyclohexane-2-acetic acid. An isomer of the degradation product of abieti acid. **11,** 234

Banerjee D. K. and **Sivanandaiah** K. M. On the stereoselective synthesis of estrone. **L5,** 20

Banerjee D. K., **Dutta** J., **Rao** A. S. and **Jacobs** E. J. Synthetic investigation on the building of ring A of steroids. **8,** 163

Banerjee D. K., **Paul** V. and **Balasubramanian** S. K. The total synthesis of 8-isotestosterone. **L12,** 23

Bapat D. S., **Rao** B. C. S., **Unni** M. K. and **Venkataraman** K. The action of diborane and of sodium borohydride-boron trifluoride-etherate on anthraquinones: a new synthesis of aloe-emodin and citreorosein and a general method for the reduction of anthraquinones to anthracene derivatives. **L5,** 15

Barnard D., **McSweeney** G. P. and **Smith** J. F. The reaction of ozone with organic hydroperoxides. **L14,** 1

Bartell L. S. Secondary isotope effects and mass-sensitive amplitudes of vibration. **L6,** 13

1960

Bartlett P. D. see **Traylor** T. G. **L24,** 30
Basinski J. E. see **Griffin** G. W. **L3,** 13
Battersby A. R. and **Harper** B. J. T. Rate study on the incorporation of tyrosine into morphine, codeine and thebaine. **L27,** 21
Battiste M. see **Breslow** R. **L26,** 42
Bauer M. see **Muller** E. **L13,** 30
Bell R. A. see **Johnson** W. S. **L12,** 27
Benkeser R. A., **Agnihotri** R. K. and **Burrous** M. L. Reduction of organic compounds by lithium in low molecular weight amines. Highly selective lithium-amine reducing systems. **L16,** 1
Benkeser R. A., **Liston** T. V. and **Stanton** G. M. Substituent effects in aromatic substitution. **L15,** 1
Benz, E. see **Wittig** G. **10,** 37
Berglund C. see **Lawesson** S,-O. **L2,** 4
Bergmann E. D. and **Cohen** S. Organic fluorine compounds. Fluorine derivatives of mevalolactone. **L8,** 20
Bergmann E. D. and **Yaroslavsky** S. Experiments in the 4-aryl-cycloalk-2-en-1-one series—IV. 4-Phenylcyclohepta-1,3-dione. **11,** 154
Bergmann E. D. see **Yaroslavsky** S. **11,** 158
Beringer F. M., **Forgione** P. S. and **Yudis** M. D. Diarylodonium salts—XII. The phenylation of dimedone, dibenzoylmethane and tribenzoylmethane. **8,** 49
Bernasconi R. see **Conroy** H. **L6,** 1
Bernatek E. and **Ledaal** T. Solvolysis of ozonides **L26,** 30
Berry R. W. H., **Brocklehurst** P. and **Burawoy** A. Electronic spectra of organo molecules and their interpretation—VII. The effect of terminal nitro and amino groups on the electronic spectra of conjugated hydrocarbon systems. **10,** 109
Berry W. L. see **Mosby** W. L. **8,** 107
Berson J. A. Apportionments of products from unsymmetrically substituted mesomeric carbonium ions. **L16,** 17
Berson J. A. Apportionments of products from unsymmetrically substituted carbonium ions. **L23,** 38
Berti G., **Settimo** A. de and **Segnini** D. The structure of skatole dimer. New reactions of indoline derivatives. **L26,** 13
Bertin D. see **Nomine** G. **8,** 217
Bestmann H. J. C-Acylierung von Triphenylphosphin-alkylenen. Ein neuer Weg zu Ketonen. **L4,** 7
Bestmann H. J. und **Schulz** H. C-Alkylierung von Triphenylphosphin-carbomethoxy-methylen. Ein neuer Weg zur Synthese von Carbonsäuren. **L4,** 5
Bhattacharjee M. K., **Mitra** R. B., **Tilak** B. D. and **Venkiteswaren** M. R. Synthesis of heterocyclic steroids—III. An unsuccessful attempt at the synthesis of B-nor-6-thiaequilenin through 3-cyano-7-methoxy-4-oxo 1,2,3,4-tetrahydrodibenzothiophene. **10,** 215
Bhattacharyya S. C. see **Rao** A. S. **9,** 275
Bhide G. V., **Tikotkar** N. L. and **Tilak** B. D. Synthesis of heterocyclic steroids—IV. Synthesis of dl-B-nor-6-oxaequilenin. **10,** 223. V. Attempted synthesis of B-nor-6-aza-6-methylequilenin. **10,** 230
Bible R. H., Jr. The conversion of podocarpic acid to nimbiol. **11,** 22; **L9,** 20
Bickel A. F., **Knotnerus J.**, **Kooyman** E. C. and **Vegter** G. C. Bicyclanes—II. On the preparation and halogenation of bicyclo[2,2,2] octane. **9,** 230
Bickel A. F. see **Schaafsma** Y. **10,** 76
Bickelhaupt F. see **Wiesner** K. **9,** 254; **L3,** 17
Biellmann J. F., **Francetic** D. et **Ourisson** G. Effets conformationnels sur l'equilibre *cis-trans* d'α-hydrindanones. **L18,** 4; **L23,** 39
Biemann K. Application of mass spectrometry to structure problems. The carbon skeleton of sarpagine. **L15,** 9
Binh L. C. see **Jacques** J. **8,** 150; **8,** 360
Birch A. J., **Cameron** D. W., **Holloway** P. W. and **Rickards** R. W. Further examples of biological C-methylation: novobiocin and actinomycin. **L25,** 26
Birch A. J., **Hodson** H. F., **Moore** B., **Potts** H. and **Smith** G. F. Echitamine. **L19,** 36
Birch A. J., **McLoughlin** B. J. and **Smith** H. The biosynthesis of the ergot alkaloids. **L7,** 1
Birkeland S. P. see **Johnson** W. S. **L5,** 1
Bladon P. see **Potier** P. **L18,** 36
Blazejewicz L. see **Heyns** K. **9,** 67
Bloemhoff W. see **Buck** H. M. **L9,** 5
Blomquist A. T., **Meinwald** Y. C., **Bottomley** C. G. and **Martin** P. W. Dimerization in Finkelstein cyclizations. **L24,** 13
Boekelheide V., **Ceder** O., **Crabb** T., **Kawazoe** Y. and **Knowles** R. N. The structure of dihydrotoxiferine. **L26,** 1
Boekelheide V. see **Rosowsky** A. **11,** 121
Bognar R. and **Wieniawski** W. Nitrogen glycosides. N-Glycosyl derivatives of substituted rhodanines. **L6,** 10
Bogri T. see **Weisner** K. **L3,** 17
Boikess R. see **Breslow** R. **L26,** 42
Bork K. H. see **Mannhardt** H. J. **L16,** 21
Borisov A. E. see **Nesmeyanov** A. N. **L3,** 25; **L8,** 23
Bottomley C. G. see **Blomquist** A. T. **L24,** 13
Bowers A., **Denot** E. and **Urquiza** R. *Cis* addition of fluorine to a steroid olefin. A new route to 6α-fluoro-Δ^4-3-ketones. **L20,** 34
Bowers A, **Denot** E., **Urquiza** R. and **Sanchez-Hidalgo** L. M. Steroids-CXXVI. Some fission reactions of steroid 5,6-epoxides induced by boron trifluoride etherate. **8,** 116
Bratek M. D. see **Marion** L. **L19,** 1
Braun J. C. and **Fisher** G. S. Hydroboration of β-pinene. **L21,** 9
Bregant N. see **Balenovic** K. **L6,** 20
Bregman J. see **Sondheimer** F. **L26,** 25
Breslow R., **Boikess** R. and **Battiste** M. Some cyclopropene rearrangements. **L26,** 42
Brewer H. W. see **Weisner** K. **L3,** 17

Brieger G. see **Tamelen** E. E. van. **L8,** 14
Briggs L. H. and **Cambie** R. C. Chemistry of the podocarpaceae—V. The identification of miropinic acid and isomiropinic acid from *Podocarpus ferrugineus* D. Don. **8,** 356
Briggs L. H., **Cain** B. F. and **Davis** B. R., A novel Prévost reaction. **L17,** 9
Briggs L. H., **Cain** B. F., **Cambie** R. C. and **Davis** B. R. Revised structures for mirene and kaurene. **L24,** 18
Brocklehurst P., **Burawoy** A. and **Thompson** A. R. Electronic spectra of organic molecules and their interpretation—VI. The electronic spectra of *p*-terphenyl and its derivates. **10,** 102
Brocklehurst P. and **Burawoy** A. Electronic spectra of organic molecules and their interpretation—VIII. The electronic spectra of thiobenzophenone and its derivatives. **10,** 118
Brocklehurst P. see **Berry** R. W. H. **10,** 109
Brockmann H., **Brockmann** H. Jr., **Gordon** J. J., **Keller-Schlierlein** W., **Lenk** W., **Ollis** W. D., **Prelog** V. und **Sutherland** I. O. Über die Identität von Rutilantinon mit Pyrromycinon und über die Lage der Carbo-methoxy-Gruppe in Pyrromycinonen. **L8,** 25
Brockmann H. Jr., see **Brockmann** H. **L8,** 25
Bronnert D. L. E. and **Saunders** B. C. Toxic fluorine compounds containing the C-F link—XI. Lability of the fluorine atom in 2-fluoroethanol. **10,** 160
Brook P. R. see **Conroy** H. **L6,** 1
Brown D. J. and **Jacobsen** N. W. The unique transannular methylation of 2-amino-4-hydroxypletidine. **L25,** 17
Brown P., **Burdon** J., **Smith** T. J. and **Tatlow** J. C. 5,5,5-Trifluorolaevulic acid and some derived compounds. **10,** 164
Brown R. D. and **Harcourt** R. D. A theoretical study of the chemistry of isoquinoline. **8,** 23
Brown R. F. C. see **Bachelor** F. W. **L10,** 1
Brückner K. see **Mannhardt** H. J. **L16,** 21
Bruckner V., **Karczag** A. (W.), **Körmendy** K., **Meszaros** M. und **Tomasz** J. Einfache Synthese des Pentacens. **L1,** 5
Bruun T. Siphulin, a chromanone type lichen acid. **L4,** 1
Büchi G. and **Manning** R. E. Structure of verbenalin. **L26,** 5
Büchi G. see **Bachelor** F. W. **L10,** 1
Buck H. M., **Bloemhoff** W. and **Oosterhoff** L. J. **L9,** 5
Budzikiewicz H. Bermerkungen zu der Arbeit von S. M. Bloom: "An acid stable cyclohexadienon". **L7,** 12; **L17,** 39
Burawoy A. see **Berry** R. W. H. **10,** 109
Burawoy A. see **Brocklehurst** P. **10,** 102, 118
Burdon J. see **Brown** P. **10,** 164
Burn D., **Petrow** V. and **Weston** G. O. A new reagent for the selective oxidation of steroidal allylic alcohols to $\alpha\beta$-unsaturated ketones **L9,** 14
Burns R. G. and **England** B. D. An interpretation of the kinetics of bimolecular substitution by anionic bases in alcohol-water mixtures. **L24,** 1
Burrous M. L. see **Benkeser** R. A. **L16,** 1
Buu-Hoï N. P. et **Lavit** D. Sur la synthése du dibenzo[a,i]pyrène, du tribenzo[a,e,i]pyrène, et de nouveaux homologues du naphto 2,3-a pyrène. **8,** 1
Buu-Hoï N. P., **Lavit** D. et **Chalvet** O. Les facteurs électroniques dans la réaction de formylation des hydrocarbures aromatiques condensés. **8,** 7

Cain B. F. see **Briggs** L. H. **L17,** 9; **L24,** 18
Cais M. see **Modiano** A. **L18,** 31
Cambie R. C. see **Briggs** L. H. **8,** 356; **L24,** 18
Cameron D. W. see **Birch** A. J. **L25,** 26
Campos M. de M., **Petragnani** N. and **Thome** C. The reaction of diaryl tellurides with vicdibromides. A new agent of debromination. **L15,** 5
Canonica L., **Pelizzoni** F., **Manitto** P. and **Jommi** G. Structure of gentiopicroside. **L24,** 7
Carlon F. E. see **Nussbaum** A. L. **8,** 145
Caserio M. C., **Graham** W. H., and **Roberts** J. D. Small-ring compounds—XXIX. A reinvestigation of the solvolysis of cyclopropylcarbinyl chloride in aqueous ethanol. Isomerization of cyclopropylcarbinyl. **11,** 171
Ceder O. see **Boekelheide** V. **L26,** 1
Cesca S. see **Giannini** U. **L14,** 19
Chakravarti D., **Chakravarti** R. N., **Ghose** R. and **Robinson** R. Echitamine. **L10,** 10
Chakravarti D., **Chakravarti** R. N., **Ghose** R. and **Robinson** R. The structure of echitamine (Addendum). **L11,** 25; **L12,** 33
Chakravarti R. N. see **Chakravarti** D. **L10,** 10; **L11,** 25; **L12,** 33
Chalvet O. see **Buu-Hoï** N. P. **8,** 7
Chandross E. A. and **Smolinsky** G. The rearrangement of 1-azido-1,2,3-triphenylcyclopropene to 4,5,6-triphenyl-*v*-triazine. **L13,** 19
Chissick S. S., **Dewar** M. J. S. and **Maitlis** P. M. New heteroaromatic compounds containing two boron atoms. **L23,** 8
Chiurdoglu G. et **Descamps** M. Contribution à l'étude des composes sesquiterpéniques—IV. Etude de la structure du carotol, alcool $C_{15}H_{26}O$ de l'essence de *Daucus Carota*. **8,** 271
Choudhuri S. N. see **Sengupta** P. **10,** 45
Church R. F., **Ireland** R. E. and **Marshall** J. A. The stereospecific total synthesis of dl-8β-carbomethoxy-13-oxopodocarpane, a degradation product of phyllocladene. **L17,** 1
Clar E. Asymmetric annellation effects—IV. Dibenzacenes. **9,** 202
Clar E. and **McCallum** A. The significance of benzenoid rings for the stability of aromatic hydrocarbons. **10,** 171
Clar E., **Fell** G. S. and (in part) **Richmond** M. H. 4,5:12,13-Dibenzoheptazethrene and 5,6:8,9:14,15:17,18-tetrabenzoheptacene. **9,** 96
Clar E., **Fell** G. S., **Ironside** C. T. and **Balsillie** A. Benzologues and other derivatives of peropyrene. **10,** 26

Clemo G. R. Further aspects of the chemistry of cigarette smoke—II. **11,** 11
Closs G. L. and **Closs** L. E. Addition of chlorocarbene to benzene. **L10,** 38
Closs G. L. and **Closs** L. E. Phenylcarbene from benzylchloride and N-butyllithium. **L24,** 26
Closs L. E. see **Closs** G. L. **L10,** 38; **L24,** 26
Cocker W. and **McMurry** T. B. H. Stereochemical relationships in the eudesmane (selinane) group of sesquiterpenes. **8,** 181
Coe P. L., **Patrick** C. R. and **Tatlow** J. C. Aromatic polyfluoro-compounds—V. The preparation of highly fluorinated benzenes by defluorination of polyfluoro- cyclohex-anes, -enes, and -dienes. **9,** 240
Cohen S. see **Bergmann** E. D. **L8,** 20
Cohen S. see **Kaluszyner** A. **11,** 252
Conroy H. Biogenesis of *Lycopodium* alkaloids. **L10,** 34
Conroy H., **Bernasconi** R., **Brook** P. R., **Ikan** R., **Kurtz** R. and **Robinson** K. W. The structure of echitamine. **L6,** 1
Cookson R. C., **Hudec** J. and **Williams** R. O. Rearrangements of oxodicyclopentadienes. **L22,** 29
Cossee P. On the reaction mechanism of the ethylene polymerization with heterogeneous Ziegler–Natta catalysts. **L17,** 12
Cossee P. The formation of isotactic polypropylene under the influence of Ziegler-Natta catalysts. **L17,** 17
Coulson C. A. and **Golebiewski** A. Molecular deformation in cyclooctadecanonaene. **11,** 125
Coulson C. A. see **Ali** M. A. **10,** 41
Crabb T. see **Boekelheide** V. **L26,** 1
Craven B. M. The molecular structure and absolute configuration of picrotoxinin. **L19,** 21
Cremer S. and **Srinivasan** R. A photochemical synthesis of bicyclo-[2.2:0]-hexane. **L21,** 24
Cross B. E., **Galt** R. H. B. and **Hanson** J. R. Gibberellin A_7. A new fungal gibberellin. **L15,** 18
Cross B. E., **Galt** R. H. B. and **Hanson** J. R. Gibberellin A9. **L23,** 22

Davis B. R. see **Briggs** L. H. **L17,** 9; **L24,** 18
Deenen L. L. M. van. see **Haas** G. H. de. **L9,** 1; **L22,** 7
Delobelle J. see **Fetizon** M. **L9,** 16
Denot E. see **Bowers** A. **8,** 116; **L20,** 34
Descamps M. see **Chiurdoglu** G. **8,** 271
Deulofeu V. see **Ondetti** M. A. **L1,** 18
Dev S. Studies in sesquiterpenes-XVI. Zerumbone, a monocyclic sesquiterpene ketone. **8,** 171; The proton magnetic resonance spectra of some sesquiterpenes and the structure of humulene. **9,** 1
Dev S. see **Nayak** U. R. **8,** 42
Dev S. see **Rao** M. V. R. K. **L27,** 27
Dewar M. J. S. and **Schmeising** H. N. Resonance and conjugation—II. Factors determining bond lengths and heats of formation. **11,** 96
Dewar M. J. S. see **Chissick** S. S. **L23,** 8
Dobinson F. and **Bailey** P. S. Effect of solvents upon the initial ozone attack on polycyclic aromatics. **L13,** 14
Doering W. von E. and **Kirmse** W. The absolute configuration of *trans*-1,2-dimethylcyclopropane. **11,** 272
Doering W. von E. and **Mole** T. Cyclopropenes from carbenes and acetylenes. Stereoselectivity in the reaction of carbomethoxycarbene with *cis*-butene. **10,** 65
Doering W. von E. and **Wiley** D. W. Heptafulvene (methylene-cycloheptatriene). **11,** 183
Doering W. von E. see **Kirmse** W. **11,** 266
Dolby L. J. see **Tamelen** E. E. van. **L19,** 30
Dolejs L., **Mironov** A. and **Sorm** F. Structure of bulnesol. Stereochemistry of guaiol, nepetalinic acids and iridomyrmecins. **L11,** 18
Downing D. F. see **Baker** W. **L5,** 6
Dulova V. G. see **Volpin** M. E. **8,** 33
Duran A. see **Fraga** F. **11,** 78
Dutta J. see **Banerjee** D. K. **8,** 163
Dytham R. A. and **Weedon** B. C. L. Organic reactions in strong alkalis—III. Fission of keto- and hydroxy-acids. **8,** 246—IV; Rearrangement and fission of acids with α-glycol and other vicinal oxygen functions. **9,** 246
Dytham R. A. see **Ackmann** R. G. **8,** 239

Earl J. C. Carbon-carbon bond energies. **9,** 65
Eaton P. see **Yates** P. **L11,** 5
Eckell A. see **Huisgen** R. **L12,** 1; 5
Ecles W. T. An X-ray study of the configuration of cevine. **L7,** 24
Eliel E. E. The absolute configuration of (+)-3-methyl-t-butyl-1-chloroallene. **L8,** 16
Ellis J., **Jackson** A. H., **Kenner** G. W. and **Lee** J. Porphyrin nuclear magnetic resonance spectra. **L2,** 23
England B. D. see **Burns** R. G. **L24,** 1
Erdtman H. see **Akiyoshi** S. **9,** 237
Evans R. J. see **Wiberg** K. B. **8,** 313

Fahrenholtz S. R. see **Saunders** W. H. **L18,** 1
Farkas L. and **Varady** J. Direkt-synthese des Irigenins. **L20,** 23
Farnum D. G. see **Yates** P. **L17,** 22
Fava A. and **Iliceto** A. Direct nucleophilic substitution in homologous series. Transmission of polar effects along a hydrocarbon chain. **L12,** 18
Fava A. see **Iliceto** A. **L11,** 27
Fell G. S. see **Clar** E. **9,** 96; **10,** 26
Fetizon M. et **Delobelle** J. La synthèse totale de l'éther méthylique du nimbiol (±) méthoxy-6 méthyl-7 podocarpatriène-5,7,13 (14). **L9,** 16
Fielding B. C., **Haws** E. J., **Holker** J. S. E., **Powell** A. D. G., **Robertson** A., **Stanway** D. N. and **Whalley** W. B. Monascorubrin. **L5,** 24
Fieser L. F. and **Fieser** M. Steroid nomenclature. **8,** 360
Filar L. J. and **Winstein** S. Preparation and behavior of simple quinone methods. **L25,** 9

Findlay J. A. see **Babin** D. R. **L15,** 31
Fischer H. und **Grob** C. A. Synchrone *Cis*-eliminierung bei der Fragmentierung von Syn α-Amino-acetophenon-oximen. **L26,** 22
Fisher G. S. see **Braun** J. C. **L21,** 9
Fleischer H. see **Rosowsky** A. **11,** 121
Fleischmann R. see **Huisgen** R. **L21,** 1
Floyd A. J. see **Baker** W. **L5,** 6
Fodor G. see **Romeike** A. **L22,** 1
Foffani A., **Pecile** C. and **Ghersetti** S. Infra-red intensity measurements on diazo-compounds. **11,** 285
Forbes E. J., **Stacey** M., **Tatlow** J. C. and **Wragg** R. T. The synthesis of 1-, 2- and 3-trifluoromethyl carbazoles by the Fischer-indole method. **8,** 67
Forbes E. J., **Tatlow** J. C. and **Wragg** R. T. The unequivocal syntheses of 2- and 4-trifluoromethyl carbazoles via diphenyls. **8,** 73
Forbes E. J. and **Wragg** R. T. The syntheses of 2- and 4-trifluoromethyl carbazoles via diphenylamines. **8,** 79
Forgione P. S. see **Beringer** F. M. **8,** 49
Forrest T. P. see **Babin** D. R. **L15,** 31
Foster R. The absorption spectra of molecular complexes. **10,** 96
Fraga F., **Gavilán** J. M., **Durán** A., **Seoane** E. and **Ribas** I. Papilionaceous alkaloids—XXXVIII. Contribution to the chemistry and stereochemistry of retamine. **11,** 78
Francetic D. see **Balenovic** K. **L6,** 20
Francetic D. see **Biellmann** J. F. **L18,** 4; **L23,** 39
Frankel M. and **Moses** P. Syntheses of amino alkyl sulphonic acids and their peptide analogues. **9,** 289
Frankel M., **Knobler** Y. and **Zvilichowsky** G. Aminoöxy-peptide derivatives of DL-canaline. **L18,** 28
Fray G. I. and **Robinson** R. Synthesis of analogues of the iridolactones. **9,** 295
Fray G. I., **Jaeger** R. H. and **Robinson** R. Synthesis of royal jelly acid. **L4,** 15
Fray G. I., **Morgan** E. D. and **Robinson** R. Synthesis of *cis*-10-hydroxydec-2-enoic acid. **L13,** 34
Fredga A. Steric correlations by the quasi-racemate method. **8,** 126
Freudenberg K. und **Sidhu** G. S. Die absolute Konfiguration des Sesamins und Pinoresinols. **L20,** 3
Freudenberg K. und **Weinges** K. Systematik und Nomenklatur der Flavonoide. **8,** 336
Fridrichsons J. and **Mathieson** A. McL. The molecular structure and absolute configuration of thelepogine methiodide. **L26,** 18
Fridrichsons J., **Mathieson** A. McL., and **Sutor** D. J. The molecular structure and absolute configuration of jacobine bromhydrin. **L23,** 35
Fried F. see **Babin** D. R. **L15,** 31
Fritz H. P., **McOmie** J. F. W. and **Sheppard** N. The infra-red spectrum of $[C_4H_4.Ag]NO_3$. **L26,** 35
Fuchs B. and **Loewenthal** H. J. E. The contraction of ring A in 5α-cholestane derivatives. **11,** 199
Gall J. S. see **Winstein** S. **L2,** 31; **L9,** 24
Galt R. H. B. see **Cross** B. E. **L15,** 18; **L23,** 22
Gaoni Y. see **Sondheimer** F. **L26,** (25)
Gates M. see **Roe** A. M. **11,** 148
Gavilán J. M. see **Fraga** F. **11,** 78
Getoff, N. **Scholes** G. and **Weiss** J. Reduction of carbon dioxide in aqueous solutions under the influence of radiation. **L18,** 17
Ghersetti S. see **Foffani** A. **11,** 285
Ghose R. see **Chakravarti** D. **L10,** 10; **L11,** 25; **L12,** 33
Giannini U. and **Cesca** S. Cyclopentadienyltrimethyltitanium. **L14,** 19
Gilbert B. see **Baker** W. **L5,** 6
Gilman H., **Peterson** D. J., **Jarvie** A. W. and **Winkler** H. J. S. The formation of dodecaphenylcyclohexasilane from the reaction of dichlorodiphenylsilane with sodium and with lithium. **L23,** 5
Ginsburg D. see **Pauncz** R. **9,** 40
Giora A. C. see **Hauptmann** H. **L11,** 1
Glover D. J. see **Kamlet** M. J. **L27,** 17
Godtfredsen W. O. see **Liisberg** S. **9,** 149
Gogte V. N., **Palkar** V. S. and **Tilak** B. D. Synthesis of condensed thiophenes, diaryls and dialkyls through aryllithium and alkyllithium derivatives. **L6,** 30
Goldman G. K. see **Rao** C. N. R. **L2,** 1
Golebiewski A. see **Coulson** C. A. **11,** 125
Golubeva E. I. see **Nesmeyanov** A. N. **L3,** 25
Gopinath K. W., **Govindachari** T. R. and **Rajappa** S. Synthesis of calycanine. **8,** 291
Gopinath K. W., **Govindachari** T. R. and **Rao** U. R. The alkaloids of *Zanthoxylum rhetsa* DC. **8,** 293
Gordon J. J., **Jackmann** L. M., **Ollis** W. D. and **Sutherland** I. O. Aklavinone. **L8,** 28
Gordon J. J. see **Brockmann** H. **L8,** 25
Gottlieb O. R. see **Lavie** D. **L22,** 23
Götz M. see **Babin** D. R. **L15,** 31
Götz M. see **Wiesner** K. **9,** 254
Gouterman M. and **Wagnière** G. Bond alternation in cyclooctadecanonaene (CON). **L11,** 22
Govindachari T. R., **Lakshmikantham** M. V., **Pai** B. R. and **Rajappa** S. Chemical examination of *Tylophora asthmatica*—III. The complete structure of tylophorine. **9,** 53
Govindachari T. R. see **Gopinath** K. W. **8,** 291; **8,** 293
Graham W. H. see **Caserio** M. C. **11,** 171
Grant P. K. and **Hodges** R. The structure of isophyllocladene. **8,** 261
Grashey R., **Huisgen** R. und **Leitermann** H. 13-Dipolare Additionen der Nitrone. **L12,** 9
Gray A. H. see **Valenta** Z. **L20,**25
Griffin G. W., **Basinski** J. E. and **Vellturo** A. F. Photodimerization of maleic and fumaric acid derivatives. **L3,** 13

Gripenberg J. Fungus pigments—XII. The structure and synthesis of thelephoric acid. **10,** 135
Grob C. A. und **Jenny** F. A. Mechanistische Uebergaenge bei der Solvolyse von γ-Aminopropylchloriden. **L23,** 25
Grob C. A. see **Fischer** H. **L26,** 22
Gut M. see **Melera** A. **L14,** 13
Gut M. see **Noller** C. R. **L15,** 15

Haas G. H. de, and **Deenen** L. L. M. van. Synthesis of a "mixed-acid" α-lecithin. **L9,** 1
Haas G. H. de and **Deenen** L. L. M. van. Partial synthesis of "mixed-acid" L-α-lecithins. **L22,** 7
Hamamoto K. see **Takeda** K. **L3,** 1
Hankwitz R. see **Lingens** F. **L20,** 7
Hansen K. F. see **Mondon** A. **L14,** 5
Hansen R. L. see **Winstein** S. **L25,** 4
Hanson J. R. see **Cross** B. E. **L15,** 18; **L23,** 22
Harcourt R. D. see **Brown** R. D. **8,** 23
Harper B. J. T. see **Battersby** A. R. **L27,** 21
Harrison W. F. see **Anderson** A. G. **L2,** 11
Hauptmann H. und **Giora** A. C. Acetessigsäuredithioketale. **L11,** 1
Havinga E., **Kock** R. J. de, and **Rappoldt** M. P. The photo-chemical interconversions of provitamin D, lumisterol, previtamin D, and tachysterol. **11,** 276
Haws E. J. see **Fielding** B. C. **L5,** 24
Henderson R. and **Hodges** R. Ketones derived from phyllocladene. **11,** 226
Herout V. see **Krepinsky** J. **L3,** 9; **L7,** 9
Herran J. see **Perezamador** M. C. **L7,** 30
Hertog H. J. den; see **Plas** H. C. van der. **L1,** 13
Heyns K. und **Blazejewicz** L. Katalytische Oxydation von primären und sekundären Hydroxylverbindungen mit Sauerstoff am Platin kontakt in flüssiger Phase. Über katalytische Oxydationen—XIV. **9,** 67
Himoe A. see **Stock** L. M. **L13,** 9
Hinman R. L. and **Lang** J. The position of protonation and basicities of indoles. **L21,** 12
Hirai S. see **Nagata** W. **L17,** 27
Hodges R. and **Reed** R. I. The stereochemistry of manoyl oxide. **10,** 71
Hodges R. see **Grant** P. K. **8,** 261
Hodges R. see **Henderson** R. **11,** 226
Hodson H. F. see **Birch** A. J. **L19,** 36
Hojo M. see **Winstein** S. **L22,** 12
Holker J. S. E. see **Fielding** B. C. **L5,** 24
Holloway P. W. see **Birch** A. J. **L25,** 26
Hudec J. see **Cookson** R. C. **L22,** 29
Hudlicky M. The synthesis of γ-fluoroglutamic acid. **L14,** 21
Huisgen R. und **Eckell** A. 1.3-Dipolare Additionen der Azomethin-imine. **L2,** 5
Huisgen R., **Fleischmann** R. und **Eckell** A. Azomethin-imine, eine neue Klasse zwitterionischer Verbindungen. **L12,** 1
Huisgen R., **Mack** W, und **Möbius** L. Der Nach weis der Zwischenstufe bei nucleophilen aromatischen Substitutionen mit Eliminierung; zur Struktur der Arine. **9,** 29
Huisgen R. see **Grashey** R. **L12,** 9
Huisgen R. see **Sauer** J. **11,** 241

Ide A. see **Sugimoto** N. **11,** 231
Ikan R. see **Conroy** H. **L6,** 1
Iliceto A., **Fava** A. and **Mazzucato** U. Thiocyanates and isothiocyanates. Equilibrium kinetics and mechanisms of isomerization. **L11,** 27
Iliceto A. see **Fava** A. **L12,** 18
Illuminati G. see **Baciocchi** E. **L23,** 30
Ireland R. E. and **Schiess** P. W. The synthesis of dl-sandara-copimaradiene, dl-pimaradiene, and some observations on the structure of rimuene. **L25,** 37
Ireland R. E. see **Church** R. F. **L17,** 1
Ironside C. T. see **Clar** E. **10,** 26
Iverach G. G. see **Ayer** W. A. **L10,** 19

Jackmann L. M. see **Gordon** J. J. **L8,** 28
Jackson A. H. see **Ellis** J. **L2,** 23
Jacobs E. J. see **Banerjee** D. K. **8,** 163
Jacobsen N. W. see **Brown** D. J. **L25,** 17
Jacques J., **Weidmann** C. et **Binh** L. C. Structure moléculaire et activité oestrogène—XIX. Préparation stéréoselective des acides méthyl-2(méthoxy-6′-naphtyl-2′)-3 pentanoiques *thréo* et *erythro*. **8,** 150; **8,** 366
Jaeger R. H. see **Fray** G. I. **L4,** 15
Jaffé H. H. and **Orchin** M. Hybridization in carbon monoxide. **10,** 212
Janot M.-M. see **Potier** P. **L18,** 36
Jarvie A. W. see **Gilman** H. **L23,** 5
Jenny F. A. see **Grob** C. A. **L23,** 25
Johnson A. W. and **LaCount** R. B. The chemistry of ylids—V. Trialkylphosphonium fluorenylides mechanism of the Wittig reaction. **9,** 130
Johnson W. S. and **Bell** R. A. A biogenetically patterned concept for the laboratory synthesis of cyclic compounds. **L12,** 27
Johnson W. S. and **Yorka** K. V. *dl*-18-Nortestosterone. **L8,** 11
Johnson W. S., **Neeman** M. and **Birkeland** S. P. A new reaction of diazamethane with α,β-unsaturated ketones. **L5,** 1
Jommi G. see **Canonica** L. **L24,** 7
Jones D. S. see **Leplawy** M. T. **11,** 39
Joshi B. S., **Srinivasan** R., **Talavdekar** R. V. and **Venkataraman** K. Derivatives of 1,3,5-triazine—I. Condensation of *o*-hydroxybenzanilides with cyanuric chloride and fission of the triazine ring. **11,** 133

Kabachnik M. I., **Mastrukova** T. A., **Shipov** A. E. and **Melentyeva** T. A. The application of the Hammett equation to the theory of tautomeric equilibrium, thione-thiol equilibrium, acidity and structure of phosphorus thio-acids. **9,** 10
Kallos J. see **Weisner** K. **L3,** 17
Kaluszyner A. and **Cohen** S. Cyclodehydration of diphenyl-trifluoro-methyl-carbinols. **11,** 252

Kamikawa T. see **Kubota** T. **L8,** 1
Kamlet M. J. and **Glover** D. J. Substituent effects in the charge-resonance spectra of 1,1-dinitroalkane anions. **L27,** 17
Karczag A. (W). see **Bruckner** V. **L1,** 5
Karpov T. P. see **Reutov** O. A. **L19,** 6
Kawazoe Y. see **Boekelheide** V. **L26,** 1
Kelkar G. R. see **Rao** A. S. **9,** 275
Keller-Schlierlein W. see **Brockmann** H. **L8,** 25
Kenner G. W., **Sheppard** R. C. and **Stehr** C. E. Synthesis of thiazole amino-acids derived from natural peptides. **L1,** 23
Kenner G. W. see **Ellis** J. **L2,** 23
Kenner G. W. see **Leplawy** M. T. **11,** 39
Kenner J. Further considerations on oxidative processes. **8,** 350
Kent M. M. see **Spialter** L. **L5,** 11
Keplinger E. see **Balaban** A. T. **9,** 163
Khastgir H. N. see **Sengupta** P. **10,** 45; **11,** 67
Kirby E. C. and **Reid** D. H. Hydride hyperconjugation in 1(3)-methylazulenes. **L27,** 1
Kirmse W. and **Doering** W. von E. Cyclopropanes from the 1°-alkyl chlorides by α-elimination. **11,** 266
Kirmse W. see **Doering** W. von E. **11,** 272
Kitaygorodsky A. I. Calculation of conformations of organic molecules. **9,** 183
Klemer A. Die Hydrolysen-geschwindigkeit der Glykosidischen Bindungen in 4α, 6β-Bis-D-glucosido-D-glucose. **L22,** 5
Knobler Y. see **Frankel** M. **L18,** 28
Knotnerus J. see **Bickel** A. F. **9,** 230
Knowles R. N. see **Boekelheide** V. **L26,** 1
Kock R. J. de; see **Havinga** E. **11,** 276
Konigsberger C. see **Senden** K. G. van. **L1,** 7
Kooyman E. C. see **Bickel** A. F. **9,** 230
Kooyman E. C. see **Schaafsma** Y. **10,** 76
Körmendy K. see **Bruckner** V. **L1,** 5
Korte F. und **Sieper** H. Papierchromatographische Charakterisierung von Haschisch-Inhaltsstoffen. **10,** 153
Kovredov A. I. see **Nesmeyanov** A. N. **L3,** 25
Krepinsky J., **Herout** V. and **Sorm** F. The identity of jatamansone and valeranone. **L3,** 9
Krepinsky J., **Romanuk** M., **Herout** V. and **Sorm** F. Constitution of valeranone. **L7,** 9
Kubota T. and **Takeda** K. Studies on the steroidal components of domestic plants—XXI. The structure of kogagenin (Part 3) on anhydrokogagenin. **10,** 1
Kubota T., **Kamikawa** T., **Tokoroyama** T. and **Matsuura** T. On the chemical constitution of obacunone. **L8,** 1
Kubota T. see **Akiyoshi** S. **9,** 237
Kupchan S. M., **Slade** P. and **Young** R. J. Intramolecular catalysis. Facilitation of alkaline hydrolysis of alicyclic 1,2-diol monoesters. **L24,** 22
Kursanov D. N. see **Parnes** Z. N. **L21,** 20
Kursanov D. N. see **Volpin** M. E. **8,** 33
Kurtz R. see **Conroy** H. **L6,** 1
LaCount R. B. see **Johnson** A. W. **9,** 130
Lakshmikantham M. V. see **Govindachari** T. R. **9,** 53
Lang J. see **Hinman** R. L. **L21,** 12
Lavie D., **Shvo** Y. and **Gottlieb** O. R. The stereochemistry of the cucurbitacins. **L22,** 23
Lavit D. see **Buu-Hoï** N. P. **8,** 1; **8,** 7
Lawesson S.-O. and **Berglund** C. Studies of peroxycompounds. Copper salt catalyzed reactions of t-butyl perbenzoate with benzyl ethers. **L2,** 4
Lawton R. G. see **Tamelen** E. E. van. **L19,** 30
Ledaal T. see **Bernatek** E. **L26,** 30
Lee J. see **Ellis** J. **L2,** 23
Leitermann H. see **Grashey** R. **L12,** 9
Lenk W. see **Brockmann** H. **L8,** 25
Leonard N. J. and **Martell** M. J., Jr. Laboratory realization of the Schöpf-Oechler scheme in vasicine synthesis. **L25,** 44
Leplawy M. T., **Jones** D. S., **Kenner** G. W. and **Sheppard** R. C. Peptides—XI. Synthesis of peptides derived from alpha-methylalanine. **11,** 39
Lewis G. E. Photocatalysed cyclisation of azobenzene. **L9,** 12
Lewis G. E. Structures of the mono-acid cations of 4-aminoazobenzene and its derivatives. **10,** 129
Lichtin N. N. see **Price** E. **L18,** 10
Liisberg S., **Godtfredsen** W. O. and **Vangedal** S. Reaction of polyhalomethanes with enolethers of Δ^4-3-ketosteroids. A new pathway to 6α-methyl-steroids. **9,** 149
Linden R. van der. see **Stewart** R. **L2,** 28
Lingens F. und **Hankwitz** R. Synthese von Acetamido-methylenbernsteinsäure. **L20,** 7
Link K. P. see **Schroeder** C. **L13,** 23
Linstead O. see **Ackmann** R. G. **8,** 221
Lipscomb W. N. see **Penfold** B. R. **L6,** 17
Lipscomb W. N. see **Wunderlich** J. A. **11,** 219
Liston T. V. see **Benkeser** R. A. **L15,** 1
Lloyd P. F. and **Stacey** M. Reactions of 2-(2′,4′-dinitro-phenyl)-amino-2-deoxy-D-glucose (DNP-D-glucosamine) and derivatives. **9,** 116
Loewenthal H. J. E. see **Fuchs** B. **11,** 199
Löw M. The conformation of cyclopentane. **L1,** 3
Lowe J. P. see **Saunders** W. H. **L18,** 1

Mack W. see **Huisgen** R. **9,** 29
MacMillan J., **Seaton** J. C., and **Suter** P. J. Plant hormones—I. Isolation of gibberellin A, and gibberellin A_5 from *Phaseolus multiflorus*. **11,** 60
Mahapatra S. N. see **Banerjee** D. K. **11,** 234
Maitlis P. M. see **Chissick** S. S. **L23,** 8
Majer J. R. Dyes containing the indole ring I. Trinuclear pentamethincyanines. **9,** 106; II Trinuclear trimethincyanines. **9,** 111
Malyanov V. A. see **Reutov** O. A. **L19,** 6
Mandell L., **Nussbaum** A. L. and **Oliveto** E. P. The structure of neoruscogenin. **L19,** 25
Manitto P. see **Canonica** L. **L24** 7

Mannhardt H. J., **Werder** F. v., **Bork** K. H., **Metz** H. und **Brückner** K. Darstellung von 16-Methylen-steroiden der Corticoid- und Progesteronreihe. **L16,** 21
Manning R. E. see **Büchi** G. **L26,** 5
Marion L., **Wiewiorowski** M. and **Bratek** M. D. The structure of angustifoline. **L19,** 1
Marshall J. A. see **Church** R. F. **L17,** 1
Martell M. J., Jr. see **Leonard** N. L. **L25,** 44
Martin P. W. see **Blomquist** A. T. **L24,** 13
Marton J. see **Ötvos** L. **L2,** 15
Mastrukova T. A. see **Kabachnik** M. I. **9,** 10
Mathieson A. McL. see **Fridrichsons** J. **L23,** 35; **L26,** 18
Mathieu J. see **Velluz** L. **9,** 145
Matsuura T. see **Kubota** T. **L8,** 1
Mazzanti G. see **Natta** G. **8,** 86
Mazzucato U. see **Iliceto** A. **L11,** 27
McCallum A. see **Clar** E. **10,** 171
McCoy C. R. see **Allred** A. L. **L27,** 25
McLoughlin B. J. see **Birch** A. J. **L7,** 1
McMurry T. B. H. see **Cocker** W. **8,** 181
McOmie J. F. W. see **Fritz** H. P. **L26,** 35
McSweeney G. P. see **Barnard** D. **L14,** 1
Mechoulam R. see **Sondheimer** F. **L22,** 38
Meinwald Y. C. see **Blomquist** A. T. **L24,** 13
Meisel-Agoston J. see **Ötvos** L. **L2,** 15
Meisels A. see **Sondheimer** F. **9,** 139
Melentyeva T. A. see **Kabachnik** M. I. **9,** 10
Melera A., **Gut** M. and **Noller** C. R. Structure of cucurbitacin B. **L14,** 13
Melera A. see **Noller** C. R. **L15,** 15
Men J. le see **Potier** P. **L18,** 36
Meszaros M. see **Bruckner** V. **L1,** 5
Metz H. see **Mannhardt** H. J. **L16,** 21
Minato H. see **Takeda** K. **L22,** 33
Miquel J. F. Molecular structure and estrogenic activity—I. Unsymmetrical diphenylethylenes and triphenylethylenes. **8,** 205
Mironov A. see **Dolejs** L. **L11,** 18
Misiti D. see **Rosnati** V. **9,** 175
Mitra R. B. see **Bhattacharjee** M. K. **10,** 215
Mizukami S. Stereochemical relations between lycorine, caranine, pluviine and lycorenine. **11,** 89
Möbius L. see **Huisgen** R. **9,** 29
Modiano A. and **Cais** M. The synthesis of two dihydropentalenyl derivatives. **L18,** 31
Mole T. see **Doering** W. von E. **10,** 65
Mondon A. und **Hansen** K. F. Zur stereochemie der Erythrinane. **L14,** 5
Montanari F. The stereochemistry of nucleophilic addition of thiophenols to propriolic acid and ethyl propiolate. **L4,** 18
Moore B. see **Birch** A. J. **L19,** 36
Moore C. G. and **Porter** M. The reaction of 2,4-dinitrobenzene-sulphenyl chloride with organic monosulphides. **9,** 58
Morgan E. D. see **Fray** G. I. **L13,** 34
Mosby W. L. and **Berry** W. L. Products of nucleophilic displacement reactions in the anthraquinone series. **8,** 107
Moses P. see **Frankel** M. **9,** 289
Mothes K. see **Reinbothe** H. **L25,** 32
Muller E., **Bauer** M. und **Rundel** W. Katalysierte Homologisierung cycloaliphatischer Ketone mit Diazomethan. **L13,** 30
Muller G. see **Velluz** L. **9,** 145
Müller W. see **Plieninger** H. **L11,** 15
Murray R. W. The reaction of dichlorocarbene with anthracene. **L7,** 27
Murray R. W. see **Saunders** M. **11,** 1

Nagata W., **Terasawa** T., **Hirai** S. und **Takeda** K. Totalsynthetische untersuchungen der Steroide Totalsynthese des rac. Pregnan- und Androstan-derivatives. **L17,** 27
Nair P. M., **Srinivasan** R. and **Verkataraman** K. Condensation of 2,4-dinitrochlorobenzene with *o*-hydroxyarylamides. **11,** 140
Natta G. and **Mazzanti** G. Organometallic complexes as catalysts in ionic polymerizations **8,** 86
Nayak U. R. and **Dev** S. **8,** 42
Neeman M. see **Johnson** W. S. **L5,** 1
Nenitzescu C. D. see **Balaban** A. T. **10,** 55; **L2,** 7
Nesmeyanov A. N., **Borisov** A. E., **Kovredov** A. I. and **Golubeva** E. I. Reactions of free radicals and unsymmetrical organo-mercuric compounds. **L3,** 25
Nesmeyanov A. N., **Borisov** A. E. and **Novikova** N. V. Geometrical isomers of stibinous and stibinic propenyl compounds. **L8,** 23
Nesmeyanov A. N., **Perevalova** E. G. and **Nikitina** T. V. Azoferrocene. **L1,** 1
Nettleton H. R. see **Wasserman** H. H. **L7,** 33
Nield E. and **Tatlow** J. C. Polyfluoro-aromatic compounds. III. Tetra- and tri-fluoro-*p*-benzoquinone. **8,** 38
Nikitina T. V. see **Nesmeyanov** A. N. **L1,** 1
Noller C. R., **Melera** A. and **Gut** M. Concerning ring A of cucurbitacin B. **L15,** 15
Noller C. R. see **Melera** A. **L14,** 13
Nomine G., **Bertin** D. et **Pierdet** A. Sur l'acces aux 16α-méthyl 17α-hydroxy stéroïdes. **8,** 217
Noszko L. see **Ötvos** L. **L2,** 19
Norikova N. V. see **Nesmeyanov** A. N. **L8,** 23
Nozoe T. and **Takeshita** H. Cuparene and cuprenene. **L23,** 14
Nussbaum A. L. and **Carlon** F. E. *Cis-trans* isomerism of steroidal $\Delta^{17(20)}$ enol acetates. **8,** 145
Nussbaum A. L. see **Mandell** L. **L19,** 25

Ohloff G. Zur thermischen Isomerisation von Citral. **L11,** 10
Ohshiro S. Studies on the syntheses of hydrogenated quinolines and iso-quinolines as analgesics—XVII. The steric structure of N-methyl-8-aza-des-N-morphinan. **8,** 304; XVIII. Synthesis of 3-hydroxy-N-methyl-8-aza-des-N-morphinan (4-Methyl-9-hydroxy-5.10b-trimethylene-1,2,3,4,4a,5,6,-10b-octahydrobenzo[F]quinoline). **10,** 175
Ohshiro S. see **Sugimoto** N. **8,** 296

Oliveto E. P. see **Mandell** L. **L19,** 25
Ollis W. D. see **Baker** W. **L5,** 6
Ollis W. D. see **Brockmann** H. **L8,** 25
Ollis W. D. see **Gordon** J. J. **L8,** 28
Ondetti M. A. and **Deulofeu** V. Alkaloids from *Aspidosperma australe* Müll. Argov. (Note II). The structure of olivacane and *u*-alkaloid C (guatambuine). **L1,** 18
Oosterhoff L. J. see **Buck** H. M. **L9,** 5
Orchin M. see **Jaffé** H. H. **10,** 212
Orr D. E. see **Wiesner** K. **L16,** 11
Ötvos L., **Marton** J. and **Meisel-Ágoston** J. Investigation of the reaction between isocyanates and acid anhydrides with ^{14}C. **L2,** 15
Ötvos L. and **Noszko** L. Investigation of the pyrolytic decarboxylation of carboxylic acids with ^{14}C. Mechanism of the formation of camphor from homocamphoric acid. **L2,** 19
Ourisson G. et **Rassat** A. Réduction du camphre par les métaux dissous. Obtention sélective d'isobornéol. **L21,** 16
Ourisson G. see **Biellmann** J. F. **L18,** 4; **L23,** 39

Padma N. see **Balasubramanian** M. **L14,** 23
Pai B. R. see **Govindachari** T. R. **9,** 53
Palkar V. S. see **Gogte** V. N. **L6,** 30
Papadopoulas S. see **Valenta** Z. **L20,** 25
Parnes Z. N., **Volpin** M. E. and **Kursanov** D. N. New types of hydride transfer. **L21,** 20
Partch R. see **Rosowsky** A. **11,** 121
Patrick C. R. see **Coe** P. L. **9,** 240
Paudler W. W. see **Taylor** E. C. **L25,** 1
Paul V. see **Banerjee** D. K. **L12,** 23
Pauncz R. and **Ginsburg** D. Conformational analysis of alicyclic compounds—I. Considerations of molecular geometry and energy in medium and large rings. **9,** 40
Pecile C. see **Foffani** A. **11,** 285
Pelizzoni F. see **Canonica** L. **L24,** 7
Penfold B. R. and **Lipscomb** W. N. The structure of HCN tetramer. **L6,** 17
Pentimalli L. Researches on the aromatic azo compounds. The oxidation of *p*-dimethylamino-phenylazo-pyridines. **9,** 194
Perevalova E. G. see **Nesmeyanov** A. N. **L1,** 1
Perezamador M. C. and **Herran** J. Turbicoryn, a new glucoside obtained from the seeds of a sacred plant. **L7,** 30
Pester R. see **Treibs** W. **L17,** 5
Peterson D. J. see **Gilman** H. **L23,** 5
Peterson R. C. and **Ross** S. D. Thermal decomposition of 1-azo-bis-1-phenylethane: Acceleration by chloranil. **L23,** 18
Petragnani N. Aryl tellurium trihalides—I. **11,** 15
Petragnani N. see **Campos.** M de M. **L15,** 5
Petrow V. see **Burn** D. **L9,** 14
Pettit R. Synthesis of the thiapyrilium cation. **L23,** 11
Piattelli M. The chemistry of porphyrin *a*. Position of the formyl group. **8,** 266
Pierdet A. see **Nomine** G. **8,** 217
Plas H. C. van der, and **Hertog** H. J. den. Synthesis of the isomeric sulphonic acids of 2,6-di-*tert*-butylpyridine. **L1,** 13
Plieninger H. und **Müller** W. Indolopyrone und Pyridone. **L11,** 15
Podesva C. see **Valenta** Z. **L20,** 25
Poittevin A. see **Velluz** L. **9,** 145
Porai-Koshits B. A. The structure of aromatic diazo-compounds. **11,** 30
Porter M. see **Moore** C. G. **9,** 58
Potier P., **Men** J. le, **Janot** M.-M. and **Bladon** P. The isolation of spermidine by degradation of lunarine. **L18,** 36
Potts H. see **Birch** A. J. **L19,** 36
Powell A. D. G. see **Fielding** B. C. **L5,** 24
Preis S. see **Schroeder** C. **L13,** 23
Prelog V. see **Brockmann** H. **L8,** 25
Price E. and **Lichtin** N. N. Ionization and dissociation equilibria of some triphenylchloromethane derivatives in nitrobenzene at 25°. **L18,** 10

Raab G. see **Seyferth** D. **L22,** 20
Rajappa S. see **Gopinath** K. W. **8,** 291
Rajappa S. see **Govindachari** T. R. **9,** 53
Ramachandran J. see **Rao** C. N. R. **L2,** 1
Rao A. S., **Kelkar** G. R. and **Bhattacharyya** S. C. Terpenoids—XXI. The structure of costunolide, a new sesquiterpene lactone from costus root oil. **9,** 275
Rao A. S. see **Banerjee** D. K. **8,** 163
Rao B. C. S. see **Bapat** D. S. **L5,** 15
Rao C. N. R., **Ramachandran** J. and **Goldman** G. K. Substituent and solvent effects on the $n \rightarrow \pi^*$ ($U \leftarrow A$) transition in aliphatic carbonyl derivatives: evidence for hyperconjugation in the excited states of molecules. **L2,** 1
Rao G. S. R. S. see **Row** L. R. **L27,** 12
Rao G. S. K. see **Rao** M. V. R. K. **L27,** 27
Rao M. V. see **Anet** F. A. L. **L20,** 9
Rao M. V. R. K., **Rao** G. S. K. and **Dev** S. Syntheses in the cadinane series: synthesis of (±)-cadinene dihydrochloride. **L27,** 27
Rao P. N. and **Axelrod** L. R. Synthesis of 2-hydroxyestradiol-17β. **10,** 144
Rao U. R. see **Gopinath** K. W. **8,** 293
Rappoldt M. P. see **Havinga** E. **11,** 276
Rassat A. see **Ourisson** G. **L21,** 16
Re G. D. An application of the semi-empirical MO-LCAO method to indoxazene and anthranil. **10,** 81
Reed R. I. see **Hodges** R. **10,** 71
Reid D. H. see **Kirby** E. C. **L27,** 1
Reinbothe H. and **Mothes** K. Ureide biosynthesis in higher plants. **L25,** 32
Reutov O. A. **Karpov** T. P., **Uglova** E. V. and **Malyanov** V. A. The mechanism of isotope exchange reactions of dialkylmercury and alkylmercuric halides. **L19,** 6
Ribas I. see **Fraga** F. **11,** 78
Richmond M. H. see **Clar** E. **9,** 96
Rickards R. W. see **Birch** A. J. **L25,** 26
Ripperger H. see **Schreiber** K. **L27,** 9
Roberts J. D. see **Caserio** M. C. **11,** 171

Robertson A. see **Fielding** B. C. **L5,** 24
Robinson K. W. see **Conroy** H. **L6,** 1
Robinson R. see **Chakravarti** D. **L10,** 10; **L11,** 25; **L12,** 33
Robinson R. see **Fray** G. I. **9,** 295; **L4,** 15; **L13,** 34
Roe A. M. and **Gates** M. A degradation of gelsemine. **11,** 148
Rogers E. F. see **Valenta** Z. **L10,** 26
Romanuk M. see **Krepinsky** J. **L7,** 9
Romeike A. and **Fodor** G. The biogenesis of hyoscine in *Datura stramonium L.* **L22,** 1
Rosa J. see **Ballester** M. **9,** 156
Rosnati V. and **Misiti** D. 2-Aryl-4-methyl-4-chlorocarbonyi-oxymethyl-2-oxazolines. Chemical reactivity and infra-red. spectra **9,** 175
Rosowsky A., **Fleischer** H., **Young** S. T., **Partch** R., **Saunders** W. H. and **Boekelheide** V. Molecular orbital calculations on some non-classical aromatics. **11,** 121
Ross S. D. see **Peterson** R. C. **L23,** 18
Row L. R. and **Rao** G. S. R. S. A new triterpene carboxylic acid from *Terminalia tomentosa* Wight *et* Arn. **L27,** 12
Rundel W. see **Muller** E. **L13,** 30
Russell G. A. Solvent effects in the reactions of free radicals and atoms—VI. Separation of polar and resonance effects in the reactions of chlorine atoms. **8,** 101
Russell R. C. see **Baker** W. **L5,** 6
Russi S. see **Ballio** A. **9,** 125

Sahini V. E. see **Balaban** A. T. **9,** 163
Sanchez-Hidalgo L. M. see **Bowers** A. **8,** 116
Sarin P. S. and **Seshadri** T. R. New components of *Citrus aurantium* **8,** 64
Sarma K. G. see **Aghoramurthy** K. **L16,** 4; **L23,** 38
Sauer J., **Huisgen** R. und **Sturm** H. J. Zur Acylierung von 5-Aryl-tetrazolen; ein Duplikationsverfahren zur Darstellung von Polyarylen. **11,** 241
Saunders B. C. see **Bronnert** D. L. E. **10,** 160
Saunders M. and **Murray** R. W. The reaction of dichlorocarbene with amines. **11,** 1
Saunders W. H., Jr., **Fahrenholtz** S. R. and **Lowe** J. P. The effect of the leaving group on orientation in E2 elimination reactions. **L18,** 1
Saunders W. H. see **Rosowsky** A. **11,** 121
Savedoff L. G. see **Winstein** S. **L9,** 24
Schaafsma Y., **Bickel** A. F. and **Kooyman** E. C. Free-radical reactions involving sulphur compounds—III. Photolysis of aromatic disulphides. **10,** 76
Schenck G. O. und **Steinmetz** R. Neuartige durch Benzophenon photosensibilisierte Additionen von Maleinsäureanhydrid an Benzol und andere Aromaten. **L21,** 1
Schiess P. W. see **Ireland** R. E. **L25,** 37
Schlogl K. und **Seiler** H. Ein zweifach überbrücktes Ferrocen. **L7,** 4
Schmeising H. N. see **Dewar** M. J. S. **11,** 96
Scholes G. see **Getoff** N. **L18,** 17
Schreiber K. und **Adam** G. Synthese von Solanum-alkaloiden aus 3β-Acetoxy-5α-pregn-16-en-20-on. **L27,** 5
Schreiber K. und **Ripperger** H. Absolute Konfiguration des Steroidalkaloids Solanocapsin an C-25. **L27,** 9
Schroeder C., **Preis** S. and **Link** K. P. The mechanism of warfarin formation from 4-hydroxycoumarin and β-anilino-benzylacetone. Evidence for Schiff base intermediates showing enhanced reactivity in the Michael reaction. **L13,** 23
Schulz H. see **Bestmann** H. J. **L4,** 5
Seaton J. C. see **MacMillan** J. **11,** 60
Segnini D. see **Berti** G. **L26,** 13
Seiler H. see **Schlogl** K. **L7,** 4
Senden K-G. van, and **Konigsberger** C. Hydrolysis of benzylidene aniline in the presence of cetyl trimethyl ammoniumbromide. **L1,** 7
Sengupta P., **Choudhuri** S. N. and **Khastgir** H. N. Terpenoids and related compounds—I. Constituents of the trunk bark of *Melia azadirachta* Linn, and the structure of the ketophenol, nimbiol. **10,** 45
Sengupta P., **Sengupta** S. K. and **Khastgir** H. N. Terpenoids and related compounds—II. Investigations on the structure of nimbin. **11,** 67
Sengupta S. K. see **Sengupta** P. **11,** 67
Seoane E. see **Fraga** F. **11,** 78
Serota S. see **Wall** M. E. **10,** 238; **11,** 131
Seshadri T. R. see **Aghoramurthy** K. **L16,** 4; **L23,** 38
Seshadri T. R. see **Sarin** P. S. **8,** 64
Settimo A. da see **Berti** G. **L26,** 13
Seyferth D., **Wada** T. and **Raab** G. The reaction of organolithium reagents with perfluorovinyl derivatives of tin and silicon. **L22,** 20
Sharma M. Synthesis of two stereo-isomers of dehydroabietic acid. **L23,** 1
Shaw P. E. see **Turner** R. B. **L18,** 24
Sheppard N. see **Fritz** H. P. **L26,** 35
Sheppard R. C. see **Kenner** G. W. **L1,** 23
Sheppard R. C. see **Leplawy** M. T. **11,** 39
Shipov A. E. see **Kabachnik** M. I. **9,** 10
Shoolery J. N., **Verzele** M. and **Alderweireldt** F. On the structure of humulinone. **9,** 271
Shvo Y. see **Lavie** D. **L22,** 23
Sidhu G. S. see **Freudenberg** K. **L20,** 3
Sieper H. see **Korte** F. **10,** 153
Simmons D. L. see **Weisner** K. **L3,** 17; **L15,** 23
Simon W. see **Sommer** P. F. **L20,** 18
Sivanandaiah K. M. see **Banerjee** D. K. **L5,** 20
Skowrońska-Serafin B. and **Urbanski** T. Preparation of derivatives of amidineurea and their reactions. **10,** 12
Slade P. see **Kupchan** S. M. **L24,** 22
Sleiter G. see **Baciocchi** E. **L23,** 30
Smith F. and **Stephen** A. M. Diborane reduction of carboxyl groups in carbohydrates. **L7,** 17
Smith G. F. see **Birch** A. T. **L19,** 36
Smith H. see **Birch** A. J. **L7,** 1
Smith J. and **Thomson** R. H. Diquinones—I.

The oosproein-tomichaedin degradation. **10,** 148
Smith J. and **Thomson** R. H. Spinochrome E. **L1,** 10
Smith J. F. see **Barnard** D. **L14,** 1
Smith P. A. S. and **Antoniades** E. P. The interplay of steric and electronic factors affecting geometrical isomerism of diaryl ketimine derivatives. **9,** 210
Smith S. see **Winstein** S. **L9,** 24; **L22,** 12
Smith T. J. see **Brown** P. **10,** 164
Smolinsky G. see **Chandross** E. A. **L13,** 19
Sommer P. F., **Arya** V. P. und **Simon** W. Über scheinbare Dissoziationskonstanten von Carbonsäuren mit aquatorialer und axialer Lage der Carboxyl-gruppe. **L20,** 18
Sondheimer F. and **Meisels** A. Constituents of *Casimiroa edulis* Llave *et* Lex—VI. 2′,5,6-Trimethoxy-flavone, 2′5,6,7-tetramethoxy-flavone (zapotin) and 5-hydroxy-2′,6,7-trimethoxyflavone (zapotinin). **9,** 139
Sondheimer F., **Gaoni** Y. and **Bregman** J. Acetylenic oxygen heterocycles. **L26,** 25
Sondheimer F., **Mechoulam** R. and **Sprecher** M. 19-Hydroxy-10-isotestosterone. **L22,** 38
Sorm F. see **Dolejs** L. **L11,** 18
Sorm F. see **Krepinsky** J. **L3,** 9; **L7,** 9
Spialter L., **Towers** R. S. and **Kent** M. M. Novel synthesis of organo-tri- and di-fluorosilanes with aqueous hydrofluoric acid. **L5,** 11
Sprecher M. see **Sondheimer** F. **L22,** 38
Srinivasan R. see **Cremer** S. **L21,** 24
Srinivasan R. see **Joshi** B. S. **11,** 133
Srinivasan R. see **Nair** P. M. **11,** 140
Stacey M. see **Forbes** E. J. **8,** 67
Stacey M. see **Lloyd** P. F. **9,** 116
Stanton G. M. see **Benkeser** R. A. **L15,** 1
Stanway D. N. see **Fielding** B. C. **L5,** 24
Stehr C. E. see **Kenner** G. W. **L1,** 23
Steinmetz R. see **Schenck** G. O. **L21,** 1
Stephen A. M. see **Smith** F. **L7,** 17
Stevens I. D. R. see **Winstein** S. **L9,** 24
Stewart R., and **Linden** R. Van der. The deuterium isotope effect in the permanganate oxidation of aromatic trifluoromethyl alcohols. **L2,** 28
Stock L. M. and **Himoe** A. Solvent effects on the isomer distribution in the chlorination of aromatics. **L13,** 9
Streitwieser A. An LCAO treatment of the acidity of hydrocarbons. **L6,** 23
Sturm H. J. see **Sauer** J. **11,** 241
Sugimoto N. and **Ohshiro** S. Studies on the syntheses of hydrogenated quinolines and isoquinolines as analgesics—XVI. Syntheses of N-methyl-8-aza-des-N-morphinan(4-methyl 5-10b-trimethylene-1:2:3:4:4a:5:6:10b-octahydrobenzo[*f*]quinoline. **8,** 296
Sugimoto N., **Watanabe** H. and **Ide** A. The synthesis of α-amino-β-(pyrazolyl-N)-propionic acid. **11,** 231
Suginome H. Oxygen heterocycles. The structure of the isoflavanone sophorol. **L19,** 16
Suter P. J. see **MacMillan** J. **11,** 60
Sutherland I. O. see **Brockmann** H. **L8,** 25
Sutherland I. O. see **Gordon** J. J. **L8,** 28
Sutor D. J. see **Fridrichsons** J. **L23,** 35
Swain C. G. and **Bader** F. W. The nature of the structure difference between light and heavy water and the origin of the solvent isotope effect—I. **10,** 182
Swain C. G., **Bader** R. F. W. and **Thornton** E. R. A theoretical interpretation of isotope effects in mixtures of light and heavy water—II. **10,** 200
Syhora K. A novel type of the ring opening of the steroidal 16α, 17α-epoxides. **L17,** 34

Takeda K. and **Hamamoto** K. The structure of metagenin. **L3,** 1
Takeda K. and **Minato** H. Absolute configuration of guaiol. **L22,** 33
Takeda K. see **Kubota** T. **10,** 1
Takeda K. see **Nagata** W. **L17,** 27
Takeshita H. see **Nozoe** T. **L23,** 14
Talavdekar R. V. see **Joshi** B. S. **11,** 133
Tamelen E. E. van, **Brieger** G. and **Untch** K. G. Synthesis of a borepin. **L8,** 14
Tamelen E. E. van, **Dolby** L. J. and **Lawton** R. G. A biogenetically-patterned laboratory synthesis in the strychnine-curare alkaloid series. **L19,** 30
Tamm C. see **Volpp** G. **L27,** 31
Tatlow J. C. see **Brown** P. **10,** 164
Tatlow J. C. see **Coe** P. L. **9,** 240
Tatlow J. C. see **Forbes** E. J. **8,** 67; **8,** 73
Tatlow J. C. see **Nield** E. **8,** 38
Taub D. see **Wendler** N. L. **11,** 163
Taylor E. C. and **Paudler** W. W. Photodimerization of some α-,β-unsaturated lactams. **L25,** 1
Terasawa T. see **Nagata** W. **L17,** 27
Ternbah M. see **Valenta** Z. **L10,** 26
Thome C. see **Campos** M. de M. **L15,** 5
Thompson A. R. see **Brocklehurst** P. **10,** 102
Thomson R. H. see **Smith** J. **10,** 148; **L1,** 10
Thornton E. R. see **Swain** C. G. **10,** 200
Tikotkar N. L. see **Bhide** G. V. **10,** 233; 230
Tilak B. D. Carcinogenesis by thiophene isosters of polycyclic hydrocarbons. Synthesis of condensed thiophenes. **9,** 76
Tilak B. D. see **Bhattacharjee** M. K. **10,** 215
Tilak B. D. see **Bhide** G. V. **10,** 223; 230
Tilak B. D. see **Gogte** V. N. **L6,** 30
Tokoroyama T. see **Kubota** T. **L8,** 1
Tomasz J. see **Bruckner** V. **L1,** 5
Towers R. S. see **Spialter** L. **L5,** 11
Traylor T. G., and **Bartlett** P. D. O^{18} tracer evidence of the termination mechanism in the autoxidation cumene. **L24,** 30
Treibs W. und **Pester** R. Butin-(2)-diol-(1,4)-poly-methylenäther. **L17,** 5
Trifan D. S. and **Bacskai** R. The role of iron in carbonium ion reactions of ferrocene derivatives. **L13,** 1
Trotter J. Bond lengths in benzene derivatives. Hybridization or resonance. **8,** 13

Turner R. B. and **Shaw** P. E. The total synthesis of a degradation product of phyllocladene. **L18,** 24

Uglova E. V. see **Reutov** O. A. **L19,** 6
Uma M. see **Baliah** V. **L25,** 21
Unni M. K. see **Bapat** D. S. **L5,** 15
Untch K. G. see **Tamelen** E. E. van. **L8,** 14
Urbański T. see **Skowrońska-Serafin** B. **10,** 12
Urquiza R. see **Bowers** A., **8,** 116; **L20,** 34

Valenta Z. and **Wright** I. G. The structure and chemistry of hydroxylycoctonine. **9,** 284
Valenta Z., **Gray** A. H., **Papadopoulas** S. and **Podesva** C. The structure of quassin. **L20,** 25
Valenta Z., **Yoshimura** H., **Rogers** E. F., **Ternbah** M. and **Wiesner** K. The structure of selagine. **L10,** 26
Valenta Z. see **Babin** D. R. **L15,** 31
Valenta Z. see **Yoshimura** H. **L12,** 14
Vangedal S. see **Liisberg** S. **9,** 149
Varady J. see **Farkas** L. **L20,** 23
Vegter G. C. see **Bickel** A. F. **9,** 230
Vellturo A. F. see **Griffin** G. W. **L3,** 13
Velluz L., **Muller** G., **Mathieu** J. et **Poitteven** A. Accès à quelques *gem*-méthoxy-hydroperoxydes stéroïdes. **9,** 145
Venkataraman K. see **Bapat** D. S. **L5,** 15
Venkataraman K. see **Joshi** B. S. **11,** 133
Venkataraman K. see **Nair** P. M. **11,** 140
Venkiteswaren M. R. see **Bhattacharjee** M. K. **10,** 215
Verzele M. see **Shoolery** J. N. **9,** 271
Volpin M. E., **Kursanov** D. N. and **Dulova** V. G. New mutual conversion of aromatic systems Tropilium salts and benzene. **8,** 33
Volpin M. E. see **Parnes** Z. N. **L21,** 20
Volpp G. and **Tamm** C. 1α,11α-Epoxy-steroids from ouabagenin by transannular substitution. **L27,** 31

Wada T. see **Seyferth** D. **L22,** 20
Wagnière G. see **Gouterman** M. **L11,** 22
Wakefield B. J. see **Ackmann** R. G. **8,** 221; **8,** 239
Walker R. W. see **Wendler** N. L. **11,** 163
Wall M. E. and **Serota** S. Steroidal sapogenins—LXII: 12-Methyl hemiketals derived from 12-keto-16-dehydropregnenes. **10,** 238; **11,** 131
Wasserman H. H. and **Nettleton** H. R. Indole ring formation from β,β-diphenylethyleneazobenzene. **L7,** 33
Watanabe H. see **Sugimoto** N. **11,** 231
Weedon B. C. L. see **Ackmann** R. G. **8,** 221; **8,** 239
Weedon B. C. L. see **Dytham** R. A. **8,** 246; **9,** 246
Weidmann C. see **Jacques** J. **8,** 150; **8,** 366
Weinges K. Die Lignane des Überwallungsharzes der Fichte. **L20,** 1
Weinges K. see **Freudenberg** K. **8,** 336
Weiss J. see **Getoff** N. **L18,** 17
Wendler N. L. D-homosteroids. Boat conformation of the D-ring. **11,** 213
Wendler N. L., **Taub** D. and **Walker** R. W. Equilibrium relationships of D-homo ketolic systems. **11,** 163
Werder F. v. see **Mannhardt** H. J. **L16,** 21
Weston G. O. see **Burn** D. **L9,** 14
Whalley W. B. see **Fielding** B. C. **L5,** 24
Wiberg K. B. and **Evans** R. J. The kinetics of the chromic acid oxidation of diphenylmethane **8,** 313
Wieniawski W. see **Bognar** R. **L6,** 10
Wiesner K. and **Orr** D. E. The structure of pithecolobine. **L16,** 11
Wiesner K., **Bickelhaupt** F., **Babin** D. R. and **Götz** M. The structure of delphinine. **9,** 254
Wiesner K., **Brewer** H. W., **Simmons** D. L., **Babin** D. R., **Bickelhaupt** F., **Kallos** J. and **Bogri** T. The structure of neoline. **L3,** 17
Wiesner K., **Simmons** D. L. and **Wightman** R. H. The configuration of delphinine. **L15,** 23
Wiesner K. see **Babin** D. R. **L15,** 31
Wiesner K. see **Valenta** Z. **L10,** 26
Wiesner K. see **Yoshimura** H. **L 12,** 14
Wiewiorowski M. see **Marion** L. **L19,** 1
Wightman R. H. see **Wiesner** K. **L15,** 23
Wiley D. W. see **Doering** W. von E. **11,** 183
Williams R. O. see **Cookson** R. C. **L22,** 29
Wilson R. D. Naphthaquinones—II. Derivatives of naphthalene-2,7-diol. **11,** 256
Winkler H. J. S. see **Gilman** H. **L23,** 5
Winstein S. and **Gall** J. S. Racemization and radio-chloride exchange of *p*-chlorobenzhydryl chloride in acetone. **L2,** 31
Winstein S. and **Hansen** R. L. An octahydrodimethanonaphthyl non-classical homocyclopropenyl cation. **L25,** 4
Winstein S., **Hojo** M. and **Smith** S. Ion pairs, racemization, chloride exchange and the mass law effect in solvolysis of *p*-chlorobenzhydryl chloride. **L22,** 12
Winstein S., **Savedoff** L. G., **Smith** S., **Stevens** I. D. R. and **Gall** J. S. Ion pairs, nucleophilicity and salt effects in bimolecular nucleophilic substitution. **L9,** 24
Winstein S. see **Filar** L. J. **L25,** 9
Wittig G. und **Benz** E. Triptycen aus Dehydrobenzol und Anthracen. **10,** 37
Wragg R. T. see **Forbes** E. J. **8,** 67; **8,** 73; **8,** 79
Wright I. G. see **Valenta** Z. **9,** 284
Wunderlich J. A. and **Lipscomb** W. N. The structure of 2,4-dibromomenthone. **11,** 219

Yang D-D. H. see **Yang** N. C. **L4,** 10
Yang N. C. and **Yang** D- D. H. Photochemical reactions of 20-ketosteroids. **L4,** 10
Yao-Tseng H. Experiments on the synthesis of substances related to tetracyclines. **11,** 52
Yaroslavsky S. and **Bergmann** E. D. Substituted 6,7-benzocoumaran-2-ones from the Stobbe reaction of benzyl ketones. **11,** 158
Yaroslavsky S. see **Bergmann** E. D. **11,** 154

Yates P. and **Eaton P.** Isomerizations in the dicyclopentadiene series. **L11,** 5
Yates P. and **Farnum** D. G. Heterocycle formation in the reaction of α-diazoacetophenone with bases. **L17,** 22
Yorka K. V. see **Johnson** W. S. **L8,** 11
Yoshimura H., **Valenta** Z. and **Wiesner** K. A rigorous proof of the selagine structure. **L12,** 14
Yoshimura H. see **Valenta** Z. **L10,** 26
Young R. J. see **Kupchan** S. M. **L24,** 22
Young S. T. see **Rosowsky** A. **11,** 121
Yudis M. D. see **Beringer** F. M. **8,** 49

Zaoral M. and **Arnold** Z. A novel peptide synthesis. **L14,** 9
Zvilichowsky G. see **Frankel** M. **L18,** 28

1960

Tetrahedron Letters No. 1, pp. 1-2, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

AZOFERROCENE

A. N. Nesmeyanov, E. G. Perevalova and T. V. Nikitina

U.S.S.R. Academy of Sciences, Moscow

(Received 1 December 1959)

IT has been reported that all attempts to prepare azo-derivatives of ferrocene either by direct coupling of diazonium salts with ferrocene, or indirectly from aminoferrocene via ferrocenyldiazonium, were unsuccessful.

As shown by the authors,[1,2] and later by Broadhead and Pauson,[3] and Weinmayr,[4] ferrocene treated with diazonium salts in an acid medium yields nothing but arylated ferrocenes. Diazotization of aminoferrocene destroyed completely the ferrocene nucleus of the molecule.[5]

A direct synthesis of methyl- and phenylazoferrocene from methyl- and phenylazocyclopentadienyllithium has been recently described by Knox.[6]

---

1 A. N. Nesmeyanov, E. G. Perevalova, R. V. Golovnya and O. A. Nesmeyanova, Dokl. Akad. Nauk SSSR 97, 459 (1954).

2 A. N. Nesmeyanov, E. G. Perevalova and R. V. Golovnya, Dokl. Akad. Nauk SSSR 99, 539 (1954).

3 G.D. Broadhead and P.L. Pauson, J. Chem. Soc. 367 (1955).

4 V. Weinmayr, J. Amer. Chem. Soc. 77, 3012 (1955).

5 A. N. Nesmeyanov, E. G. Perevalova, R. V. Golovnya and L. S. Shilovtseva, Dokl. Akad. Nauk SSSR 102, 535 (1955).

6 G. R. Knox, Proc. Chem. Soc. 56 (1959).

The authors succeeded in preparing azoferrocene by treating lithioferrocene[7] with N_2O under the conditions reported for phenyllithium and N_2O by Beringer et al.[8] and Meier.[9,10]

$$C_5H_5FeC_5H_4Li \xrightarrow{N_2O} C_5H_5FeC_5H_4\text{-}N = N\text{-}OLi \longrightarrow$$

$$\xrightarrow{C_5H_5FeC_5H_4Li} C_5H_5FeC_5H_4\text{-}N = N\text{-}C_5H_4FeC_5H_5$$

Azoferrocene was isolated from other reaction products chromatographically (on Al_2O_3). The yield was as high as 30% (based on unrecovered ferrocene). The compound is stable in air, soluble in ether, ligroin, benzene, ethanol, when crystallized from benzene it gives deep violet crystals m.p. 256-258° dec. - (in a sealed capillary) (Found: C 60.10; H 4.79; Fe 28.11; N 7.27. $C_{20}H_{18}Fe_2N_2$ requires C 60.34; H 4.55; Fe 28.06; N 7.03%). Ultra-violet spectrum of the compound, determined in isooctane, contains maxima at 315, 375 and 510 m (log. ϵ max. 2.55, 1.88 and 1.91).

The structure of azoferrocene was confirmed by hydrogenation on Pt-catalyst in glacial acetic acid to aminoferrocene identical with the sample previously prepared by the authors.[5]

The other products of the reaction are being studied.

---

[7] D.W. Mayo, P.D. Shaw and M. Rausch, Chem. & Ind. 1388 (1957).

[8] F.M. Beringer, J.A. Farr and A. Sauds, J. Amer. Chem. Soc. 75, 3984 (1953).

[9] R. Meier, Chem. Ber. 86, 1483 (1953).

[10] R. Meier and W. Frank, Chem. Ber. 89, 2747 (1956).

Tetrahedron Letters No. 1, pp. 3-4, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

THE CONFORMATION OF CYCLOPENTANE

M. Lőw

Institute of Organic Chemistry, University E.L., Budapest

(Received 1 December 1959)

FOR several years cyclopentane has been considered not entirely planar owing to torsional stresses between its methylene groups. Experimental investigations into the spatial structure of the molecule, although supporting the above assumption, did not lead to unequivocal conclusions.

Pitzer et al.[1] offered arguments and calculations of thermodynamical nature that cyclopentane exists in a number of continuously interchanging molecular forms. Le Fevre and Le Fevre,[2] on the other hand, produced geometric data of a rigid axial-symmetric model based on the measured polarizabilities of the molecule.

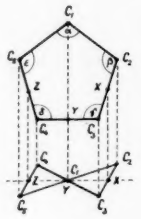
Their data, however, appear to be inconsistent with an equilateral pentagon structure of the molecule. I have therefore recalculated the

---

[1] J. E. Kilpatrick, K. S. Pitzer and R. Spitzer, J. Amer. Chem. Soc. 69, 2483 (1947); K. S. Pitzer and W. E. Donath, J. Amer. Chem. Soc. 81, 3213 (1959).

[2] C. G. Le Fevre and R. J. W. Le Fevre, Rev. Pure and Appl. Chem. 5, 261 (1955); C. G. Le Fevre and R. J. W. Le Fevre, J. Chem. Soc. 3549 (1956).

cyclopentane model of Le Fevre and Le Fevre with the polarizability values given in their paper.



The corrected values of the C-C-C angles are: $\alpha=105.91^{\circ}$; $\beta=\varepsilon=102.86^{\circ}$; $\gamma=\delta=99.20^{\circ}$. C_2, C_3, C_4 and C_5 lie alternately on both sides of the C_1XYZ plain in a distance of 0.278 Å. The Le Fevres already mention the fact in their latest paper[3] that "... the 5-ring is slightly less non-planar than previously calculated...".

Comparing the thermodynamical model with the mentioned polarizability values it seems probable that the thermodynamical model accords with the real spatial arrangement of the cyclopentane molecule. The polarizability model itself refers rather to the molecular shape distorted by the electric field, when exerted onto the molecule.

The detailed discussion of these calculations is to be published in the Acta Chim. Acad. Sci. Hung.

---

[3] C. G. Le Fevre and R. J. W. Le Fevre, J. Chem. Soc. 2340 (1959).

Tetrahedron Letters No. 1, pp. 5-6, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

EINFACHE SYNTHESE DES PENTACENS

V. Bruckner, A. Karczag (Wilhelms), K. Körmendy,

M. Meszaros und J. Tomasz

Institut für Organische Chemie, L. Eötvös Universität, Budapest

(Received 1 December 1959)

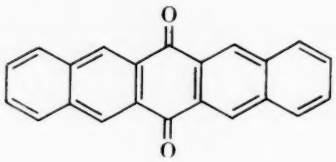
DIE bisher bekannten zwei Wege[1,2] für die Synthese des Pentacens (I) sind ziemlich umständlich und zur Hérstellung grösserer Mengen schwerlich geeignet. Wir haben gefunden, dass Pentacen-6,13-chinon (II), das sich nach Ried und Anthöfer[3] aus dem leicht zugänglichen Cyclohexan-1.4-dion und o-Phthalaldehyd äusserst einfach und auch in viel grösseren Ansätzen als dies beschrieben wurde[3] aufbauen lässt (Ausbeute an Reinprodukt rund 78% d.Th.), in siedendem Cyclohexanol durch Aluminium-tri-cyclohexoxyd zu Pentacen (I) reduzieren lässt. Letzteres scheidet sich schon aus der siedenden Lösung in gut entwickelten Kristallen aus und kann durch einfaches Waschen mit Cyclohexanol, heissem Eisessig, konz. Salzsäure und Wasser

---

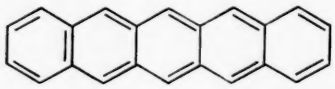
[1] E. Clar und Fr. John, Ber. 62, 3021 (1929); 63, 2967 (1930); 64, 981, 2194 (1931).

[2] W. J. Bailey und M. Madoff, J. Amer. Chem. Soc. 75, 5603 (1953).

[3] W. Ried und F. Anthöfer, Angew. Chem. 65, 601 (1953).



I



II

praktisch ohne Verlust in analysenreinen Zustand gebracht werden. Die bisher übliche Isolierung bzw. Reinigung durch eine zeitraubende Vakuumsublimierung in CO_2-Strom fällt somit fort. Durch 48 stündiges Kochen von 50 g II in einer Lösung von 50 g Aluminium in 1000 ml Cyclohexanol liessen sich 21 - 23 g (46,5-51% d.Th.) des analysenreinen Pentacens (I) herausgewinnen. Die Untersuchung der Frage, wie sich die Ausbeute durch Variierung der Versuchsbedingungen ändern lässt, ist noch im Gange.

Es ist zu vermuten, dass sich die Reduktion mit Aluminium-tricyclohexoxyd (oder anderen Alkoholaten), die erstmalig von Coffey und Boyd[4] zum Umsatz von Anthrachinon zu Anthracen angewandt worden ist, auch zur Herstellung von anderen Gliedern der Acenreihe aus den entsprechenden Chinonen oder vielleicht auch Dichinonen und Oxychinonen mit Erfolg heranziehen liesse. Es werden jetzt auch diesbezügliche Versuche durchgeführt.

Eine ausführliche Mitteilung erscheint demnächst an anderer Stelle.

---

[4] S. Coffey und V. Boyd, J. Chem. Soc. 2469 (1953).

Tetrahedron Letters No. 1, pp. 7-9, 1959. Pergamon Press Ltd. Printed in Great Britain.

1960

HYDROLYSIS OF BENZYLIDENE ANILINE IN THE PRESENCE OF CETYL TRIMETHYL AMMONIUMBROMIDE

K. G. van Senden and C. Koningsberger

Laboratory of Organic Chemistry

Technological University, Eindhoven, Netherlands

(Received 1 December 1959)

FROM investigations carried out by Robinson,[1] Schöpf,[2] Haley and Maitland[3] a.o. it is well-known that many organic reactions of the ionic type occur smoothly under physiological (or cell-possible) conditions in aqueous solution. Nevertheless, up to now this reaction medium has found hardly any practical application, owing to the very low solubility of most organic compounds in water. Several years ago we started a new research project in this field, guided by the idea that adding detergent salts to this medium would increase the solubility of the reactants. Moreover, investigations on emulsion polymerization have clearly indicated that detergent salts could be favourable used to accelerate reactions and increase yields.

We now wish to report a kinetic study of the proton catalysed reaction

---

[1] R. Robinson, J. Chem. Soc. 111, 876 (1917).

[2] C. Schöpf, Angew. Chemie 50, 779 (1937); Ibid. 50, 797 (1937).

[3] C. A. C. Haley and P. Maitland, J. Chem. Soc. 3155 (1951).

benzylidene aniline + water $\rightleftharpoons$ benzaldehyde + aniline

in a boric acid - sodium borate buffer at pH 9 and 25 $\pm$ 0.1°C. (Benzylidene aniline dissolved in methanol was added to the detergent salt buffer solution, in order to obtain in a reasonable time, a macro-homogeneous reaction medium; the final content of the latter amounted to 0.2% methanol).

The reaction can be followed most conveniently by ultraviolet spectrophotometric methods, which show that the equilibrium is shifted almost completely to the right (99.6%). The overall rate constants of the hydrolysis were determined in the presence of various amounts of the cationic detergent salt cetyl trimethyl ammoniumbromide (CTAB) and in its absence. In all cases the amount of CTAB present in solution exceeded the critical micelle concentration.

Addition of this cationic detergent salt invariably causes a considerable retardation of hydrolysis, much more than can be accounted for by normal salt effects. So far, our results are in complete agreement with those of Duynstee and Grunwald,[4] who recently described the influence of 0.01 M of detergent salts on the alkaline fading of triphenylmethane dyes and sulphonphtalein indicators.

The overall (pseudo first order) rate constants (k^*) of the hydrolysis of benzylidene aniline in the presence of different concentrations of CTAB, as measured by our method, are given in the following table:

---

[4] E. F. J. Duynstee and E. Grunwald, J. Amer. Chem. Soc. 81, 4540 (1959); Ibid. 81, 4542 (1959).

1960

mol CTAB	$k^* \times 10^3$ min^{-1}
0.00	56.5
0.01	2.82
0.02	1.53
0.03	0.97
0.04	0.76
0.05	0.62
0.06	0.51
0.07	0.44

From these data it is evident that the overall rate constant is inversely proportional to the molarity of the detergent salt at least between the limits of 0.01 and 0.07. This fact could possibly be explained by the assumption that the number of detergent molecules, associated in a "Hartley micelle" increases proportionally with increasing concentration of the detergent salt until the micelle is filled completely. At the site of the reaction (in or on the micelle) the medium may be influenced by a change in composition of the micelle, and this fact could account for the change in overall reaction rates as shown above.

Our study will be continued and published elsewhere in full detail.
We wish to thank the Netherlands Organisation for Pure Scientific Research (Z. W. O.) at the Hague for financial support of our research.

Tetrahedron Letters No. 1, pp. 10-12, 1960. Pergamon Press Ltd. Printed in Great Britain.

SPINOCHROME E

J. Smith and R. H. Thomson

Chemistry Department, The University, Aberdeen

(Received 3 December 1959)

SPINOCHROME E was first isolated, along with several other pigments, by Lederer,[1] from the calcareous parts of Mediterranean specimens of the sea urchin Paracentrotus lividus (Lam.), but insufficient material was available for chemical investigation. It has been obtained recently by Yoshida[2] from the species Psammechinus miliaris (Gemelin), in larger quantity. The pigment was isolated by treatment of the spines and test (shell) with hydrochloric acid, followed by dilution with methanol, and precipitation with pyridine. This product was then taken up in methanol, containing hydrochloric acid, from which spinochrome E separated. Recrystallization from acidified methanol gave brownish red needles, m.p. 320°. Carbon and hydrogen analysis indicated the formula $C_{10}H_{11}O_{10}$. We are greatly indebted to Dr. M. Yoshida for a gift of 200 mg. of this material.

---

[1] E. Lederer, Biochim. Biophys. Acta 9, 92 (1952).

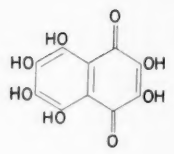
[2] M. Yoshida, J. Mar. Biol. Ass. U.K. 38, 455 (1959).

1960

The specimen received contained 2.3% N and 3.3% Cl. These impurities were probably introduced during the previous treatment. Conversion to the acetate, and subsequent hydrolysis with methanolic sulphuric acid gave material free from nitrogen and chlorine, having C, 47.0; H, 2.5%. $C_{10}H_6O_8$ requires C, 47.2; H, 2.4%. (The product of hydrolysis with methanolic hydrochloric acid gave C and H figures very similar to those of Yoshida.[2]) The pigment gave the following colour reactions:

NaOH	- deep orange, becoming green and then vanishing
$NaHCO_3$	- light brown precipitate (in MeOH)
$Na_2S_2O_4$	- decolourized, in MeOH, colour returned slowly in air
$FeCl_3$	- green (in MeOH)
$Pb(OAc)_2$	- violet precipitate (in MeOH)

Spinochrome E formed a yellow hexa-acetate, m.p. 192°, a colourless leuco-octa-acetate, m.p. 265° (decomp.), and, with diazomethane, a brown tetramethyl ether, m.p. 185°. The latter gave no colouration with aqueous sodium bicarbonate but formed a blue-violet solution in aqueous sodium hydroxide, and a violet solution with methanolic lead acetate. The ultraviolet absorption of the hexa-acetate showed maxima at 247 and 360 mμ (log ε 4.22 and 3.79 respectively) in methanol, and the curve was very similar to that of spinazarin tetra-acetate (2,3,5,8-tetra-acetoxy-1,4-naphthaquinone); the leuco-octa-acetate had $\lambda_{max.}$ 296 mμ (log ε 3.9) and $\lambda_{infl.}$ 286 mμ (log ε 3.87) (in chloroform), the spectrum closely resembling that of leucospinazarin hexa-acetate (1,2,3,4,5,8-hexa-acetoxynaphthalene). The leuco-octa-acetate has Mol. wt. 556 (ebullioscopic in benzene); octa-acetoxynaphthalene requires 592.



I

From these data we conclude that spinochrome E is hexahydroxy-naphthaquinone (I). Experiments leading to the synthesis of this c mpound will be initiated shortly.

Satisfactory analyses were obtained for all derivatives.

Tetrahedron Letters No. 1, pp. 13-17, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

SYNTHESIS OF THE ISOMERIC SULPHONIC ACIDS OF 2,6-DI-TERT.-BUTYLPYRIDINE

H.C. van der Plas and H.J. den Hertog
Laboratory of Organic Chemistry of the
Agricultural University, Wageningen, The Netherlands

(Received 7 December 1959)

SOME time ago we have shown that the sulphonic acid obtained in the remarkable sulphonation of 2,6-di-tert.-butylpyridine (I) with sulphur trioxide in liquid sulphur dioxide at -10° according to Brown and Kanner [1] is not the 4-derivative (III) as suggested by these investigators but the 3-derivative (II) [2]. Recently our conclusion was affirmed by the results of an examination of the nuclear magnetic resonance spectrum of the sulphonic acid by Muller and Wallace [3]. In this letter a definitive proof is given by syntheses of both II and III from 4-ethoxypyridine (IV) and 4-thiomethylpyridine (V) respectively.

---

[1] H.C. Brown and B. Kanner, J. Am. Chem. Soc. 75, 3865 (1953).

[2] H.C. van der Plas and H.J. den Hertog, Chem. Weekblad 53, 560 (1957).

[3] N. Muller and W.J. Wallace, J. Org. Chem. 24, 1151 (1959).

Synthesis of 2,6-di-tert.-butylpyridine-3-sulphonic acid (II).

4-Ethoxypyridine (IV) was converted with tert.-butyl lithium into 2-tert.-butyl-4-ethoxypyridine (VI. B.p. 115-116° (15 mm), n_D^{20} 1.494. Found: C, 73.7; H, 9.7. $C_{11}H_{17}NO$ requires C, 73.70; H, 9.56. Picrate m.p. 121-122°. Found: C, 50.2; H, 4.6; N, 13.6. $C_{11}H_{17}NO.C_6H_3N_3O_7$ requires C, 50.00; H, 4.94; N, 13.72).

By reacting VI with tert.-butyl lithium again, the 2,6-di-tert.-butyl derivative of 4-ethoxypyridine (VII) was obtained (b.p. 141-142°/21 mm. $HAuCl_4$ compound m.p. 193-194°. Found: C, 31.4; H, 4.4; Au, 34.0; N, 2.6. $C_{15}H_{25}NO.HAuCl_4$ requires C, 31.39; H, 4.56; Au, 34.27; N, 2.44).

Heating of VII with 25% aqueous hydrochloric acid solution yielded 2,6-di-tert.-butylpyridone-4 (VIII. M.p. 170.5-172°. Found: C, 75.2; H, 10.3; N, 6.7. $C_{13}H_{21}NO$ requires C, 75.31; H, 10.21; N, 6.77. $HAuCl_4$ compound m.p. 199-201°. Found: C, 41.5; H, 5.6; Au, 26.1. $(C_{13}H_{21}NO)_2.HAuCl_4$ requires C, 41.38; H, 5.74; Au, 26.13).

From the UV absorption spectra of VIII in absolute methanol (λ_{max}, 258 mμ; log ε, 4.17), in 0.1 N methanolic hydrochloric acid solution (λ_{max}, 240 mμ; log ε, 3.97) and in 0.1 N methanolic sodium methylate solution (λ_{max}, 232 mμ; log ε, 3.91) it seems probable that VIII chiefly occurs in the pyridone structure.

By heating with a mixture of phosphorus pentachloride and phosphorus oxychloride, VIII was converted into 2,6-di-tert.-butyl-4-chloropyridine (IX. B.p. 110-112°/12 mm. Found: C, 69.5; H, 8.9. $C_{13}H_{20}NCl$ requires C, 69.16; H, 8.93. $HAuCl_4$ compound m.p. 252-254°. Found: 27.8; H, 3.9; Au, 34.5. $C_{13}H_{20}NCl.HAuCl_4$ requires C, 27.45; H, 3.72; Au, 34.67).

1960

IX could be sulphonated according to the procedure of Brown and Kanner. The reaction rate was slow, however, the sulphonic acid X being formed in a yield of 12% only when XIII was allowed to stand with an excess of sulphur trioxide in liquid sulphur dioxide at -10° for 20 hrs. The sodium salt of 2,6-di-tert.-butyl-4-chloro-pyridine-3-sulphonic acid was isolated and melted at 304-305° (Found: C, 47.7; H, 6.0; Cl, 11.1. $C_{13}H_{19}ClNO_3SNa$ requires C, 47.64; H, 5.84; Cl, 10.82).

The chlorine atom in X was replaced by hydrogen by refluxing this substance in alkaline ethanolic solution with a Raney nickel catalyst for 4 hrs. The reaction product, 2,6-di-tert.-butylpyridine-3-sulphonic acid (II. M.p. 333-334° (with decomp.)) was identified as S-benzylthiuronium derivative (m.p. 213-215°. Found: C, 57.9; H, 7.5; N, 9.8. $C_{21}H_{31}N_3S_2O_3$ requires C, 57.64; H, 7.14; N, 9.60) with the corresponding compound of II obtained by sulphonation of 2,6-di-tert.-butylpyridine (I) with sulphur trioxide in liquid sulphur dioxide.

Synthesis of 2,6-di-tert.-butylpyridine-4-sulphonic acid (III).

4-Thiomethylpyridine (V) was converted with tert.-butyl lithium into 2-tert.-butyl-4-thiomethylpyridine (XI. B.p. 105-107° /10 mm. Found: C, 66.5; H, 8.3. $C_{10}H_{15}NS$ requires C, 66.24; H, 8.34. Picrate m.p. 113-114°. Found: C, 47.1; H, 4.4. $C_{10}H_{15}NS.C_6H_3N_3O_7$ requires C, 46.82; H, 4.42).

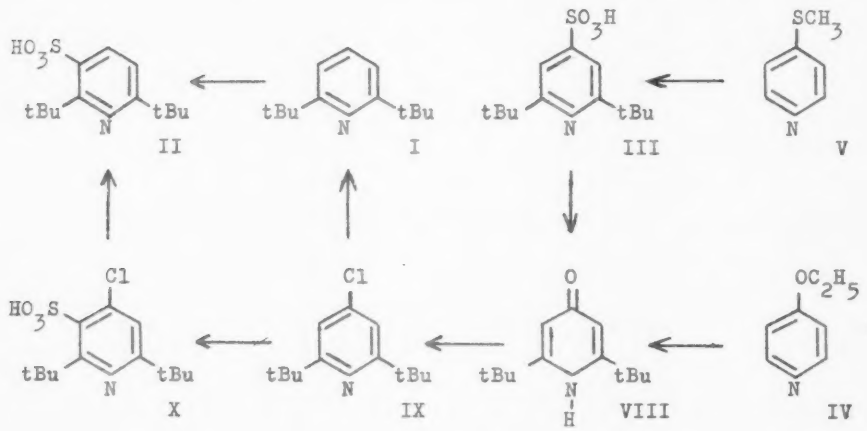
By reacting XI again with tert.-butyl lithium a complicated reaction product was obtained, containing possibly 2,6-di-tert.-butylpyridine-4-thiol (XII) and inter alia 4,4'-di-(2,6-di-tert.-butylpyridyl)sulfide (XIII, m.p. 125-126°. Found: C, 75.9; H, 9.8;

N, 6.6; S, 7.6. $C_{26}H_{40}N_2S$ requires C, 75.67; H, 9.77; N, 6.79; S, 7.77).

After removing XIII from the reaction product and oxidising the residue with a mixture of 30% aqueous hydrogen peroxide solution and acetic acid, 2,6-di-tert.-butylpyridine-4-sulphonic acid (III) was obtained.

III is a colourless substance, m.p. 344-346° (with decomp.) from a mixture of benzene and ethanol. Found: C, 57.2; H, 7.5. $C_{13}H_{21}NO_3S$ requires C, 57.51; H, 7.78 . Its S-benzylthiuronium derivative melts at 210-212° (Found: C, 58.1; H, 7.3; N, 9.4. $C_{21}H_{31}N_3O_3S$ requires C, 57.64; H, 7.14; N, 9.60).

Proof of the structures of the isomeric sulphonic acids of I:



The positions of the tert.-butyl groups in both II and III are the same as in IX, the structure of which is established by the formation of this substance from 4-ethoxypyridine (IV) and its conversion by catalytical reduction into 2,6-di-tert.-butylpyridine(I).

1960

The position of the sulphonic acid group in II follows from its formation (via X) from IX in which compound hydrogen is available for substitution only at positions 3 and 5.

The position of the sulphonic acid group in III follows from the synthesis described and the conversion of III by heating with water for 10 hrs at 240° in a sealed tube into VIII.

The conclusions given above are affirmed by the following facts:

II does not react when heated with aqueous ammonia at 160°, but yields 2,6-di-tert.-butyl-3-hydroxypyridine when heated with potassium hydroxide at 330° [4].

III is converted by heating with aqueous ammonia at 180° into 4-amino-2,6-di-tert.-butylpyridine (XV. Picrate m.p. 146-150° (with decomp.). Found: C, 52.4; H, 5.5; N, 15.9. $C_{13}H_{22}N_2.C_6H_3N_3O_7$ requires C, 52.41; H, 5.79; N, 16.09).

The UV absorption spectrum of a solution of the picrate of XV in 96% ethanol corresponds with that of 4-aminopyridine picrate solution.

The microanalyses were carried out in this laboratory by Mr. W.P. Combé.

---

[4] Cf. the paper cited in note 2.

Tetrahedron Letters No. 1, pp. 18-22, 1960. Pergamon Press Ltd. Printed in Great Britain.

ALKALOIDS FROM ASPIDOSPERMA AUSTRALE MÜLL. ARGOV. (NOTE II). THE STRUCTURE OF OLIVACINE AND U-ALKALOID C (GUATAMBUINE)

Miguel A. Ondetti and Venancio Deulofeu

Laboratorios de Investigación, E. R. Squibb and Sons Argentina S.A.

Av. Sir Alexander Fleming 1653, Martínez, Buenos Aires, Argentina

(Received 7 December 1959)

In our first note[1] we described some experiments with olivacine which lead to the conclusion that this base, isolated by Schmutz, Hunziker and Hirt[2] from A. ulei, and found by us in A. australe Müll. Argov., had a carbazol nucleus condensed with a pyridine ring; the indol-isoquinoline structure being preferred. Two methyls were also present in the alkaloid.

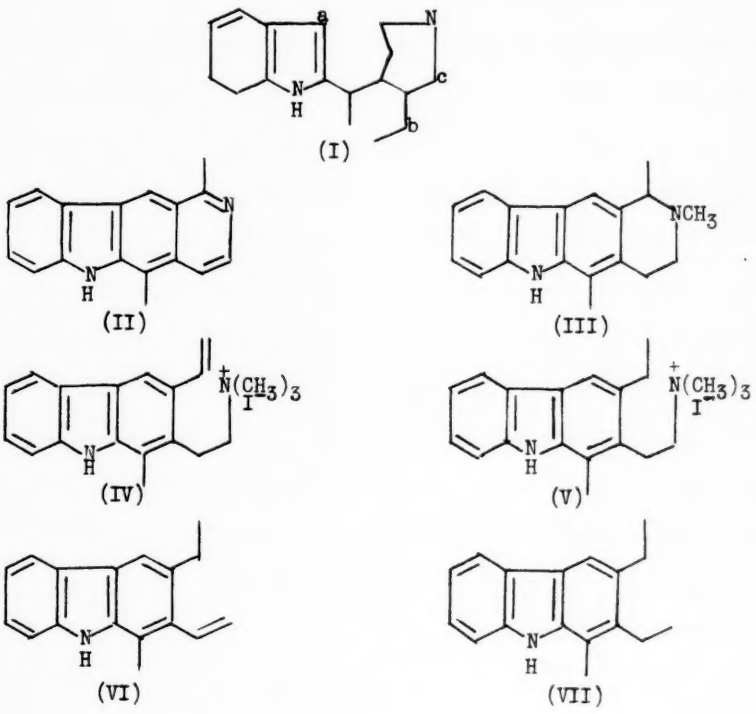
As N-methyl-tetrahydro olivacine was found to be identical with the racemic form of u-alkaloid C, a dextrorotatory base also present in both species of Aspidosperma, at least one of the methyls must be attached to the pyridine ring, as required by the existence of an asymmetric center in the last base; u-alkaloid C has also been

---

[1] M. A. Ondetti and V. Deulofeu, Tetrahedron Letters 7, 1 (1959).

[2] J. Schmutz, F. Hunziker and R. Hirt, Helv. chim. Acta 40, 1189 (1957).

1960



found in A. longepetiolatum Kuhlm[3] and given the definitive name of guatambuine.

The recent clarification of the structure of uleine by

---

[3] P. Carvalho Ferreira and G. B. Marini-Bettolo, Ann. Chim. 49, 869 (1959). P. Carvalho Ferreira, G.B. Marini-Bettolo and J. Schmutz, Experientia 15, 179 (1959).

Büchi and Warnhoff[4] and of the structure and synthesis of ellipticine by Woodward, Iacobucci and Hochstein[5], showed a relationship between both alkaloids and the latter authors proposed a common genetic intermediate (I) for both bases. Woodward and Iacobucci[6] suggested also that the same entity could be an intermediate in the formation of olivacine, for which they proposed structure (II). (Bond c-N is broken; c joins a; b joins N). If this structure is accepted, some of the products obtained by Hofmann degradation from olivacine should be identical with those from uleine.

We wish to report some degradation work done with olivacine which agrees with this point of view. From N-methyl-tetrahydro-olivacine (III), $C_{18}H_{20}N_2$, a methiodide was obtained, m.p. 298-299°, that when submitted to a Hofmann degradation gave two products. One was an unsaturated tertiary base that without further purification was transformed into a new crystalline methiodide (IV), m.p. 284-285°, which analyzed well for $C_{20}H_{25}N_2I$. Its infrared spectrum showed the characteristic bands of the vinyl group and the UV spectrum had maxima at 241 and 280 mμ.

When the unsaturated tertiary base was first hydrogenated (Platinum oxide) and the crude reduced product treated with methyl

---

[4] G. Büchi and E. W. Warnhoff, J.Am.Chem.Soc., 81,4433(1959).

[5] R. B. Woodward, G. A. Iacobucci and F. A. Hochstein, J.Amer.Chem.Soc., 81, 4434 (1959).

[6] Private communication.

1960

iodide, a different methiodide formed (V), m.p. 287-288°, which gave a typical carbazol spectrum ($\lambda_{max.}$ 240, 250, 262, 298 mμ). Although the m.p. of this methiodide could not be raised by further crystallization, it did not give any depression when mixed with a methiodide, m.p. 295-296° that was prepared by a Hofmann reaction from uleine methiodide. (Schmutz, Hunziker and Hirt[2] give m.p. 300-302°, correct.). IR-spectra of both compounds were identical.

When the above saturated methiodide derived from olivacine, m.p. 287-288°, was submitted to a second Hofmann degradation, it gave a new methine, m.p. 65-67° ($\lambda_{max.}$, 258 and 299 mμ) which gave no depression when mixed with the product, m.p. 69.5-70.5°, obtained from the similar methiodide prepared from uleine (Prof. Büchi). IR-spectra were superimposable.

By hydrogenation, this methine gave a compound (VII), m.p. 74.5-75.5°, with a carbazol spectrum ($\lambda_{max.}$: 240, 248, 261 and 298 mμ) and did not give any depression in the m.p. when mixed with a sample of the compound, m.p. 76.5-77.0° (Prof. Büchi) obtained from uleine, by a double Hofmann reaction and hydrogenation[2,4]. The IR-spectra were also identical.

(+) Guatambuine, which is N-methyltetrahydro olivacine, must then have structure (III). The fact that the methiodide of (+) guatambuine, when submitted to a Hofmann reaction gives an optically inactive methine, which methiodide is identical to that obtained from N-methyl tetrahydro olivacine (IV), is also in agreement with the proposed structure.

The second base obtained by Hofmann degradation of N-methyl-tetrahydro olivacine (III) did not change when submitted to hydrogenation. It gives a methiodide, m.p. 262-263°, with an IR-spectrum different from those recorded for the unsaturated methiodide (IV) and its reduction product (V). It has a UV-carbazol spectrum ($\lambda_{max.}$ 240, 250, 261 and 297 mμ).

Our m.p. were determined in a Kofler block and are uncorrected.

We thank Prof. R. B. Woodward for the information on the proposed structure of olivacine; Prof. B. Büchi for the generous gift of several compounds derived from uleine and for the control of some mixed m.p. and IR-spectra; Mr. J. F. Alicino and Dr. N. H. Coy, The Squibb Institute for Medical Research, New Brunswick, N.J., for the microanalysis and IR spectra.

Tetrahedron Letters No. 1, pp. 23-26, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

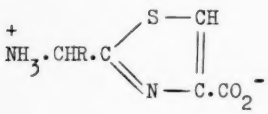
SYNTHESIS OF THIAZOLE AMINO-ACIDS DERIVED FROM NATURAL PEPTIDES

G. W. Kenner, R. C. Sheppard and C. E. Stehr

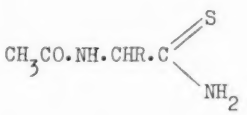
Department of Organic Chemistry, The University, Liverpool

(Received 1 December 1959)

IN connexion with our studies on the antibiotic, Thiostrepton,[1] we have prepared a number of 2-(α-aminoalkyl)-thiazole-4-carboxylic acids (I, R=H, Me, Et and $CHMe_2$). Since thiazole structures have been advanced for degradation products of other peptide antibiotics,[2,3] a brief account of our results is given here.



I



II

The thiazole amino-acids (I) were obtained by reaction of the

---

[1] J. Vandeputte and J. D. Dutcher, Antibiotics Annual 560 (1955-56).

[2] P. Brookes, A. T. Fuller and J. Walker, J. Chem. Soc. 689 (1957).

[3] J. M. Waisvisz, M. G. van der Hoeven and B. te Nijenhuis, J. Amer. Chem. Soc. 79, 4524 (1957).

appropriate acetylaminoalkylthioamides (II) with ethyl brompyruvate,[4] and subsequent hydrolysis. Purification was most readily achieved by adsorption on columns of activated charcoal and elution with aqueous phenol, a technique also useful for the isolation of thiazole amino-acids from peptide hydrolysates.

The synthetic compounds show a common ultra-violet absorption maximum at 234-5 mμ (log ε 3.72-3.76 in H_2O), while bands at 772-775 cm^{-1} in the infra-red spectra of the amino acids, and at 720-730 cm^{-1} of their hydrochlorides also appear to be characteristic. Other physical constants are collected in Table 1 (satisfactory analyses were obtained in all cases).

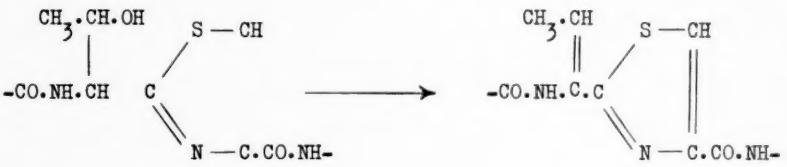
TABLE 1

I,R=	M.p. (dec.)	Hydrochloride m.p. (dec.)	R_F(A)	R_F(B)
H	277-280°	267-268.5°	0.22	0.58
Me	265-267°	233.5-234.5°	0.35	0.62
Et	256-258°		0.44	0.74
$CHMe_2$	252.5-253.5°	258-259°	0.52	0.80

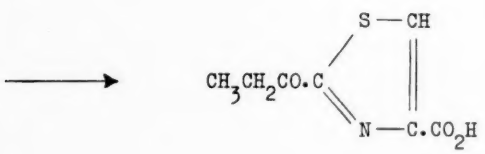
Notes: Melting points are uncorrected. Paper chromatography solvent systems: A, n-BuOH(10), EtOH(10), H_2O(5), $Et.CO_2H$(2), (Ileu, R_F=0.58); B, n-BuOH(10), Me_2CO(10), H_2O(5), dicyclohexylamine (2), (Ileu, R_F=0.64). Ninhydrin colours were yellow turning purple in A.

[4] cf. R. H. Wiley, D. C. England and L. C. Behr, Organic Reactions 6, 367 (1951).

Two of these amino acids (I, R=H and Et) are identical with hydrolysis products of Thiostrepton (apart from the question of optical acitivity in the latter case). The published infra-red data show clearly that a third ((I, R=$CHMe_2$) is the racemate of a product from the antibiotic, Micrococcin.[2] The formation of this last thiazole amino-acid has been explained[2] in terms of biogenetic modification of adjacent valine and cysteine residues to a thiazole system in the antibiotic. Our products from Thiostrepton may be similarly derived from glycine and α-aminobutyric acid respectively, but, in view of the low isolated yields (2-3%), the possibility that hydrolysis takes a more complex course than simple opening of peptide bonds must be considered. For example, thiazoles and thiazolines derived from adjacent threonine and cysteine residues might be expected to decompose in a number of ways under hydrolytic conditions, because of the activating effect of the heterocyclic ring. In particular, reverse-aldol and β-elimination reactions would be facilitated. It is noteworthy that formation of a further product



III



IV

from Micrococcin, 2-propionyl-thiazole-4-carboxylic acid (IV), is immediately explicable on the basis of elimination of the β-hydroxyl group of the "threonylthiazole" (III), prior to hydrolysis of the peptide bonds.

We hope to obtain further information on these points through synthesis of the appropriate model compounds.

1960

Tetrahedron Letters No. 2, pp. 1-3, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

SUBSTITUENT AND SOLVENT EFFECTS ON THE $n \rightarrow \pi^*$ ($^1U \leftarrow {}^1A$) TRANSITION IN ALIPHATIC CARBONYL DERIVATIVES: EVIDENCE FOR HYPERCONJUGATION IN THE EXCITED STATES OF MOLECULES

C. N. R. Rao, J. Ramachandran* and G. K. Goldman**

Department of Inorganic and Physical Chemistry, Indian Institute of Science, Bangalore, India

(Received 15 December 1959)

WE have been investigating structural and solvent effects on the $n \rightarrow \pi^*$ transition[1] of the carbonyl group, particularly in the aliphatic derivatives. It has been noted earlier[2,3] that substituents capable of donating electrons to the π-conjugated system by resonance interaction shift the $n \rightarrow \pi^*$ transition to lower wavelengths. In the $n \rightarrow \pi^*$ transition of the carbonyl group, the electronic charge is transferred from the oxygen to the carbon. Groups like the halogens, $-OCH_3$ and $-NH_2$ when attached to the carbon atom cause a very large decrease in the wavelength. Interestingly enough, aliphatic carbonyl compounds (RCOR' where R = CH_3) with R' as H, CH_3, C_2H_5, i-C_3H_7 and t-C_4H_9, show the $n \rightarrow \pi^*$ transition bands at 2910,

---

* University of California, Berkeley, Calif., U.S.A.

** Purdue University, Lafayette, Indiana, U.S.A.

1 J. W. Sidman, Chem. Rev. 58, 689 (1958).

2 A. Burawoy, J. Chem. Soc. 1177 (1939).

3 S. Nagakura, Bull. Chem. Soc. Japan 25, 164 (1952).

2765, 2775, 2835 and 2860 Å respectively in a hydrocarbon solvent. There is a large decrease in the wavelength going from R'=H to R'=CH_3 and then on there is a progressive increase in the wavelength in the series. This suggests that when both R and R' are methyl groups, there may be some type of resonance interaction by electron donation. This interaction decreases when R' is H or any other alkyl group. Inductive interaction cannot explain this trend in the wavelengths since trifluoroacetone (R'=CF_3) shows this transition at 2775 Å in o-octane. If the extra resonance interaction when both R and R' are methyl groups is considered to be by C-H hyperconjugation, then, the variation of the $n \rightarrow \pi^*$ band maximum with R' is in the Baker - Nathan order. This order is maintained in solvents of varying degree of polarity and/or hydrogen bonding. So, this trend may be taken as evidence for hyperconjugation in the excited states of molecules. We have studied this transition in a number of aliphatic ketones and a treatment similar to that of Kreevoy and Taft[4] should be possible.

In general it may be said that the effect of alkyl groups on the near ultra-violet absorption spectra of aromatic compounds is not consistent. The evidence presented from this study for resonance (possibly by hyperconjugation) in the alkyl groups in the excited states of molecules seems to be foolproof because, (i) the molecules studied are aliphatic and so no other type of resonance interaction can occur, (ii) in the molecules studied hyperconjugative resonance has been shown[5] to be unimportant in the ground state, (iii) the unusual electronic transition employed is very structure

---

[4] M. M. Kreevoy and R. W. Taft, Jr., J. Amer. Chem. Soc. 77, 5590 (1955).

[5] C. N. R. Rao, G. K. Goldman and C. Lurie, J. Phys. Chem. 63, 1311 (1959).

sensitive, and (iv) similar trends are observed in different solvents of varying degree of polarity and/or hydrogen bonding.

All the ketones show increasing solvent blue shifts[1] with the increasing polarity and/or hydrogen bonding ability of the solvent. In the series of aliphatic carbonyl compounds (RCOR' with R=CH_3), the solvent blue shift is maximum when R'=CH_3, in all the solvents studied. At least part of this effect may be due to the slightly larger permanent dipole moment of acetone compared to the other derivatives. Another explanation for this effect can be based on the extra resonance interaction of the two methyl groups which may result in a more complex charge distribution of the acetone molecule in the excited state. Then, by the Franck - Condon principle the solvation energy in the excited state of acetone will be considerably different from others.

Further work is in progress and it is hoped to publish a detailed report of the substituent and solvent effects in the near future.

We wish to thank the authorities of the Departments of Chemistry, University of California and Purdue University for providing facilities for research.

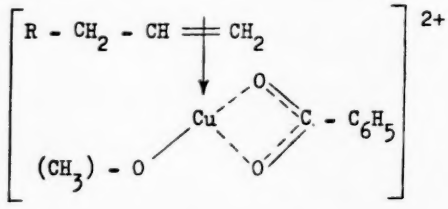
Tetrahedron Letters No. 2, pp. 4-6, 1960. Pergamon Press Ltd. Printed in Great Britain.

STUDIES OF PEROXYCOMPOUNDS. COPPER SALT CATALYZED REACTIONS OF t-BUTYL PERBENZOATE WITH BENZYL ETHERS[1]

S.-O. Lawesson and C. Berglund
Department of Organic Chemistry, Chemical Institute, University of Uppsala, Uppsala, Sweden

(Received 15 December 1959)

DURING recent years a series of publications has been produced from the late Dr. M. S. Kharasch's Institute of Organic Chemistry, dealing with the modifying influence of certain transition metal salts on homolytic reactions.[2-5] When t-butyl perbenzoate is decomposed in the presence of an olefin the benzoyloxygroup is introduced specifically into the allyl position[2] without any isomerization. A concerted mechanism has been postulated, and Denney et al.,[6] working with t-butyl perbenzoate (carbonyl O^{18}) suggest a reasonable intermediate, I, for these reactions.



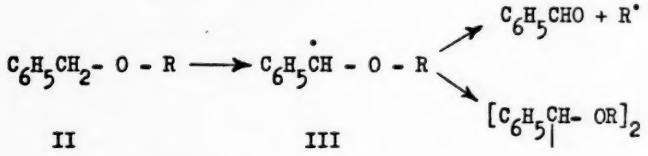
I

[1] Part III: S.-O. Lawesson and T. Busch, Acta Chem. Scand. 13, 1716 (1959).

[2] M. S. Kharasch and G. Sosnovsky, J. Amer. Chem. Soc. 80, 756 (1958).

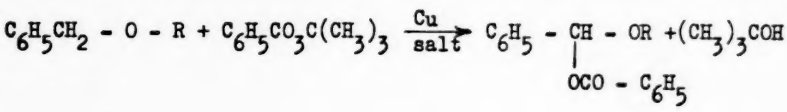
In our opinion this hypothesis, that free radicals are not completely free in the presence of copper salts, is probably correct and we are now able to present further support for this mechanism.

By decomposing t-butyl peroxide in the presence of different benzyl ethers, II, a hydrogen atom is abstracted from the ether and a radical, III, formed. Huang et al.[7,8] have shown that radical III may then either disproportionate or dimerize or both.



II III

We have now found that for different substituents R it is possible to introduce the bensoyloxygroup into ethers, and among them benzylic ethers, II, using the method of Kharasch, Sosnovsky and Fono.



IV

Irrespective of the nature of R, only benzoates, IV, could be isolated, which is a strong indication that under these conditions the radicals are not completely free.

---

[3] M. S. Kharasch and A. Fono, J. Org. Chem. 23, 324 (1958).

[4] M. S. Kharasch and A. Fono, J. Org. Chem. 24, 72 (1959).

[5] M. S. Kharasch and A. Fono, J. Org. Chem. 24, 606 (1959).

[6] D. B. Denney, D. Z. Denney and G. Feig, Tetrahedron Letters 15, 19 (1959).

[7] R. L. Huang and S. S. Si-Hoe, Proc. Chem. Soc. 354 (1957).

A full paper will be published in Arkiv for Kemi in early 1960. Additional work is in progress for a complete elucidation of these observations, with particular regard to reactions between perbenzoates and benzyl sulphides, cyclic ethers and thioethers, epoxy compounds and amines.

---

[8] R.L. Huang and S.S. Si-Hoe, in Vistas in Free Radical Chemistry (Edited by W.A.Waters) p. 242. Pergamon Press, London (1959).

Tetrahedron Letters No. 2, pp. 7-10, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

PREPARATION OF PYRYLIUM SALTS BY OLEFIN DIACYLATION. THE TWO PYRYLIUM SALTS FORMED IN AMYLENE DIACETYLATION WITH VARIOUS CATALYSTS

A. T. Balaban and C. D. Nenitzescu
Laboratory of Organic Chemistry, Polytechnical Institute, Bucharest

(Received 17 December 1959)

THE recent publication of two preliminary notes by Praill,[1] describing the formation of pyrylium salts from olefins, acid anhydrides and perchloric acid, prompts us to report the following results.

As was shown previously[2] pyrylium salts, and hence pyridines, may be prepared by Friedel - Crafts diacylation of olefins. The scope and limitations of this method were studied by variation of the acyl radical and of the olefin, using aluminium chloride, and in some cases stannic chloride, as catalyst, and isolating the pyrylium salts as perchlorates. The diacetylation of trimethylethylene (or t-amyl chloride) in the presence of $AlCl_3$ leads to 2,6-dimethyl-4-ethyl-pyrylium perchlorate, but in the presence of $SnCl_4$ no pyrylium perchlorate could be isolated.

In order to explain this difference, we studied the acetylation of amylene in various conditions, and found that in some cases the pyrylium

---

[1] P. F. G. Praill and A. L. Whitear, Proc. Chem. Soc. 312 (1959); P. F. G. Praill, Chem. & Ind. 1123 (1959).

[2] A. T. Balaban and C. D. Nenitzescu, Liebigs Ann. 625, 74 (1959).

salt formed had structure 2,6-dimethyl-4-ethyl (A) while in other cases it had structure 2,3,4,6-tetramethyl (B). These structures were assigned on the basis of the reaction with hot aqueous hydroxide (leading in case A to 3-methyl-5-ethyl-phenol,[2] and in case B to a mixture of 2,3,5- and 3,4,5-trimethylphenol) and with aqueous ammonia (pyridine A: picrate[2] m.p. 120°, chloroplatinate[2] m.p. 213°, methiodide m.p. 205°, picrolonate m.p. 215°; pyridine B: picrate m.p. 107° and 123°,[3] chloroplatinate m.p. 228°, methiodide m.p. 188°, picrolonate m.p. 225°).

The nature of the product formed in the reaction was established by isolation of the pyrylium salt (perchlorates: A m.p. 189°, B 95°; reineckeates: A m.p. 155°, B 187°; chloroantimonates: A m.p. dec. 141°, B 191°) and by treatment of the reaction mixture with aqueous ammonia to give the corresponding pyridine (characterized by its derivatives and I.R. spectrum).

It was thus found that trimethylethylene or t-amyl chloride and acetyl chloride yield only A in the presence of $SbCl_5$, $AlCl_3$, $AlCl_3$ in carbon

---

[3] The literature reports for the m.p. of 2,3,4,6-tetramethylpyridine two values: 107° [4,5] and 123°.[6,7] We established that this is a case of dimorphism, the two forms being interconvertible by seeding the melt on the Kofler hot stage, or the saturated alcoholic solution of one form, with crystals of the other.

[4] T. Eguchi, Bull. Chem. Soc. Japan 2, 176 (1927); Ibid. 3, 227 (1928).

[5] R. A. Van Meter et al., Analyt. Chem. 24, 1758 (1952).

[6] H.B. Nisbet and A.M. Pryde, J.Inst.Fuel 27, 58 (1954); Nature, Lond. 168, 832 (1951) R.J. Benzie, J.N. Milne and H.B. Nisbet, Oil Shale and Cannel Coal Vol.2, p. 784. The Institute of Petroleum, London (1951).

[7] K. Tsuda, N. Ikekawa, H. Mishima, A. Iino and T. Morishige, Pharm. Bull. 1, 122 (1953); Chem. Abstr. 49, 1719 (1955).

disulphide or in nitromethane, while trimethylethylene or t-amyl alcohol and acetic anhydride yield only or mainly B in the presence of boron fluoride etherate, perchloric acid or sulphoacetic acid. Trimethylethylene and acetic anhydride with sodium perchlorate and acetyl chloride alone or in acetic acid[8] also yield only B. The use of $ZnCl_2$ leads to B with t-amyl chloride and acetyl chloride, and to a mixture of A and B with t-amyl alcohol and acetic anhydride. Mixtures are also produced from t-amyl chloride, acetyl chloride and $TiCl_4$ or $FeCl_3$. If the reaction mixture prepared from t-amyl chloride, acetyl chloride and stannic chloride is converted directly to the pyridine, the resultant compound is found to be mainly A, but if the mixture is hydrolysed and left in conc. aqueous-ethanolic solution, the pyrylium chlorostannate B (m.p. 281°) is slowly deposited. However, unsuccessful attempts were made to effect the reaction between trimethylethylene or t-amyl chloride or alcohol and an acetylating mixture prepared from conc. aqueous hydrochloric acid, stannic chloride and acetic anhydride.[9]

These same catalysts were also applied to the diacetylation of isobutylene (introduced as t-butanol or t-butyl chloride). The following new 2,4,6-trimethylpyrylium salts were thus prepared: chloroantimonate m.p. dec. 174°, and reineckeate m.p. 165°. The preparation of 2,4,6-trimethylpyrylium perchlorate from t-butanol, acetic anhydride and perchloric acid was developed into a synthetic method[10] with average yield 55% relative to

---

[8] K. B. L. Mathur, J. N. Sharma, K. Venkataraman and H. G. Krishnamurty, J. Amer. Chem. Soc. 79, 3582 (1957).

[9] R. Jenny, C. R. Acad. Sci., Paris 248, 355 (1959).

[10] Submitted for publication to Organic Syntheses (1959).

perchloric acid. It was found that if the last reagent added to the mixture of the other two is the alcohol or the anhydride, large amounts of tri-isobutylene separating as a colourless upper layer are formed.

Experimental details and theoretical implications of this reaction will be discussed in a later paper.

Acknowledgements - We wish to thank Dr. G. V. Dinneen from the U.S. Bureau of Mines for the mixed m.p. determination of 2,3,4,6-tetramethyl-pyridinium picrate, and especially Professor H. B. Nisbet from Heriot-Watt College, Edinburgh, for the mixed m.p. determination of the picrate, methiodide and picrolonate of 2,3,4,6-tetramethylpyridine.

Tetrahedron Letters No. 2, pp. 11-14, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

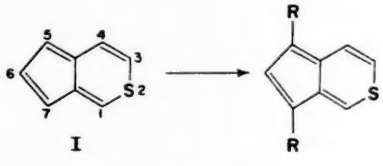
ELECTROPHILIC SUBSTITUTION IN CYCLOPENTA[C]THIAPYRAN

A. G. Anderson, Jr. and W. F. Harrison*

Department of Chemistry, University of Washington,
Seattle 5, Washington, U.S.A.

(Received 24 December 1959)

THE synthesis of cyclopenta[c]thiapyran (I) was announced in a recent communication[1] from this laboratory. The aromatic character of I, previously indicated by its thermal stability and the similarity of its ultraviolet and visible spectra to those of azulene, has now been demonstrated by successful electrophilic disubstitution. Further, strong evidence for the structures of the products has been obtained.



I

II, R = Cl
III, R = SCN
IV, R = Br
V, R = $COCH_3$

---

* National Science Foundation Predoctoral Fellow, 1959 - 1960.

1 A. G. Anderson Jr., W. F. Harrison, R. G. Anderson and A. G. Osborne, J. Amer. Chem. Soc. 81, 1255 (1959).

Reaction of I with N-chlorosuccinimide in benzene gave a dichloro substitution derivative (II), m.p. 86-87°. (Found for $C_8H_4Cl_2S$: C, 47.04; H, 1.96; Cl, 34.87) Treatment of I with thiocyanogen in carbon tetrachloride produced a dithiocyano product (III), m.p. 152-154°. (Found for $C_{10}H_4N_2S_3$: C, 48.11; H, 1.28) The dibromo compound (IV), m.p. 84-86° dec. (Found for $C_8H_4Br_2S$: C, 32.95; H, 1.62) was formed by reaction of I with N-bromosuccinimide in benzene. Acetylation of I with excess acetic anhydride in the presence of stannic chloride gave a diacetyl derivative (V), m.p. 183-184.5°. (Found for $C_{12}H_{10}O_2S$: C, 66.14; H, 4.54). Reaction of I with tetranitromethane afforded only a mononitro substitution product, m.p. 147.5-150°. (Found for $C_8H_5NO_2S$: C, 53.38; H, 2.88).

Evidence for the structures of II, III, IV and V was obtained by analysis and comparison of the NMR spectra of I, II and III (Fig. 1). Our interpretation of the spectrum of I is as follows: The triplet of unit intensity at $\tau = 2.58$[2] is assigned to the proton in the 6-position. The weakly split doublet of unit intensity at $\tau = 1.65$ is due to the proton in the 1-position and the spin-spin splitting observed is thought to arise through interaction with the proton in the 3-position.[3] The doublet of unit intensity at $\tau = 2.02$ shows no splitting from interaction with the 1-proton and is therefore assigned to the proton in the 4-position. The absorptions due to the protons in the 3-, 5- and 7- positions all lie near $\tau = 3.15$ and insofar as the spectrum can be resolved the spin-spin couplings in this region are consistent with this assignment (see Fig. 1).[4]

---

[2] $\tau = 10.00 - \delta^{int.}_{Me_4Si}$

[3] Spin-spin coupling across a sulfur atom in an aromatic system has also been reported for 3-methylthiophene; I. Weinberg, Monthly Ecumenical Letters from Laboratories of NMR No. 12, 6 (1959).

No gross difference in the electronic distribution in the ground states of I and II would be expected[5] and, thus, no large differences in

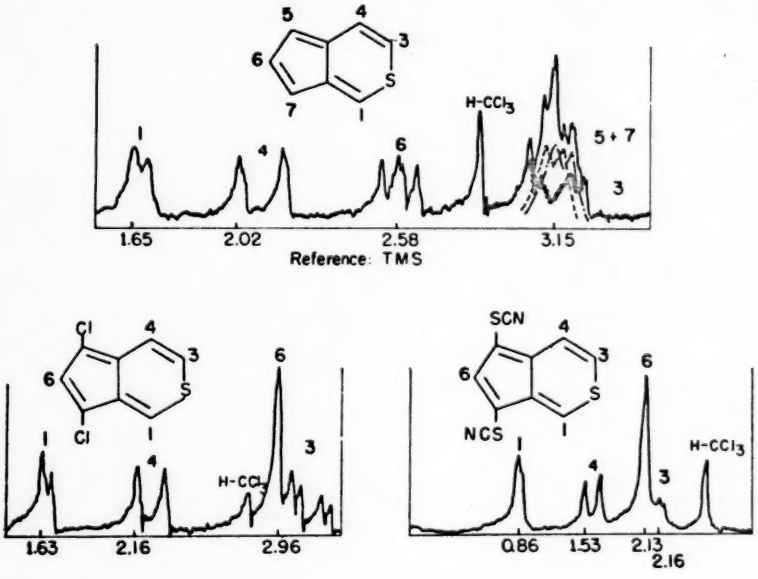


FIG. 1. NMR spectra of cyclopenta [c] thiapyran, 5,7-dichloro- and 5,7-dithiocyanocyclopenta [c]-thiapyran.

the values for the protons common to both. In the spectrum of II the doublet for the 4-proton, the doublet for the 1-proton, and the quadruplet

---

[4] The relative chemical shifts of the protons in I suggest a charge displacement in the ground state of I with a dipole vector in the direction of the five-membered ring.

[5] The ultraviolet spectra of I and II are very similar.

for the 3-proton all are found within 0.15τ of the locations in the spectrum of I. Further, the triplet assigned to the 6-proton in I is replaced by a singlet of unit intensity (τ = 2.96) in the spectrum of II.[6] Therefore II almost certainly has the structure given.[7]

The spectrum of III is also strongly in accord with the proposed 5,7-disubstituted structure. The shift of the absorption downfield could arise through inductive[8] or ring current perturbations caused by the thiocyano groups.

By analogy, the structures shown (IV and V) are the most probable ones for these disubstitution compounds. It is not yet known whether the mononitro product is the 5- or the 7-substituted derivative, or a mixture of these. Further work is in progress.

Acknowledgement - This investigation was supported in part by a research grant (NSF-G7397) from the National Science Foundation.

---

[6] The shift upfield of the absorption due to the 5-proton in II relative to I is also observed for the 2-proton in 1,3-dihaloazulenes as compared to azulene; A. G. Anderson, Jr. and L. L. Replogle, unpublished results.

[7] This conclusion is also supported by a study of the NMR spectrum of the cyclopenta [c] thiapyrillium ion in sulfuric acid and in deutero-sulfuric acid wherein it was shown that equilibrium protonation of I occurs at the 5- and 7-positions; A. G. Anderson, Jr. and W. F. Harrison, unpublished results.

[8] The electron-withdrawing nature of the thiocyano group is reflected in its σp value of +0.60; F. G. Bordwell and P. J. Bontan, J. Amer. Chem. Soc. 78, 854 (1956).

Tetrahedron Letters No. 2, pp. 15-18, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

INVESTIGATION OF THE REACTION BETWEEN ISOCYNATES AND ACID ANHYDRIDES WITH ^{14}C

L.Ötvös, J.Marton and J.Meisel-Ágoston

Central Research Institute for Chemistry of the Hungarian Academy of Sciences

(Received 15 December 1959)

THE readiness of diacylamine derivatives for transfer of the acyl group is known long ago.[1] Recently this type of compounds has been used also in acylations from a preparative point of view.[2] Generally they are obtainable by making an anhydride react with an isocyanate.[3]

$$R\text{-}N{=}C{=}O + (R'CO)_2O \longrightarrow R\text{-}N(COR')(CO R') + CO_2$$

From this point of view and especially with regard to the synthesis of radioactive diacyl derivatives, it seemed of interest to investigate the reaction with ^{14}C. The carbon atom of the liberated carbon dioxide may come either from the C=O group of the isocyanate or from one of the

---

[1] Brunner, Ber.Dtsch.Chem.Ges. 47, 2676 (1914); Monatshefte 36, 517 (1915).

[2] E.Taschner, M.Kocor and S.Meyer, Rockniki Chem. 26, 692-694 (1952) Chem.Abstr. 49, 2464 (1955).

[3] A.Wurtz, Ann.Chim. No.3. 42, 54 (1884).

carbonyls of the anhydride. In the former case if 1-^{14}C anhydride is applied, the molar activity of the product has to agree with that of the anhydride, in the latter case it should be reduced to one half of it.

Phenyl and α -naphthyl isocyanate respectively and Di-1, 1'-^{14}C-acetic anhydride have been used with our experiments. The latter compound was prepared by a method [4] evolved in this Laboratory starting from barium-1-^{14}C-acetate and 1-^{14}C-acetyl chloride. The determinations of activity were carried out with an argon-methane proportional counter for $^{14}CO_2$ gas. The results obtained are given in Table 1.

TABLE 1

Compound	Activity, μc/mM
Acetic anhydride	6538
Diacetanilid	6534
N-diacetyl-α-naphtylamine	6540

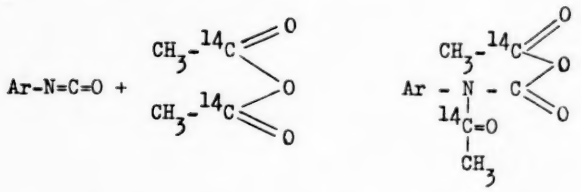
The experiments prove that, with these compounds, the CO_2 originates from the isocyanate.

The mechanism of the reaction is probably analogous to that of the addition reaction [5] between isocyanates and carboxylic acids. According to this assumption, as a first step the mixed anhydride of an N-acetylated carbaminic acid and a carboxylic acid is formed

---

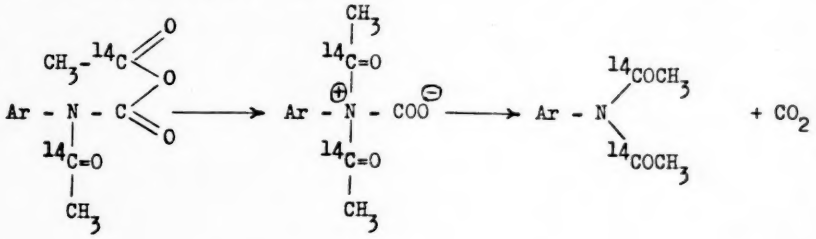
[4] L.Ötvös, J.Márton and Miesel Tiborné, KKK Közlemenyei 3 (1959).

[5] C.Naegeli and A.Tyabji, Helv. Chim. Acta 18, 142 (1935); A.Fry, J.Amer. Chem.Soc. 75, 2686 (1953).



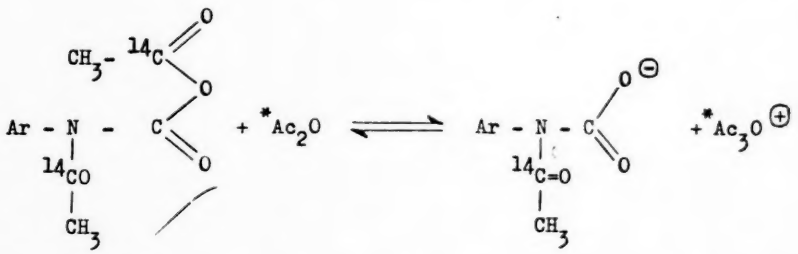
The further transformation of the intermediate product obtained may be achieved by an intramolecular (I) or intermolecular (II) transfer of the acyl group. In the latter case the compound of the anhydride type would be converted into N-acetyl carbaminic acid by acetylation of the isocyanate or more probably by a mechanism similar to that of the exchange reaction between acetic anhydride and acetyl chloride,[6] i.e. by the formation of a complex with the acetic anhydride furnishing the derivative of diacetamide by decarboxylation and acetylation.

I

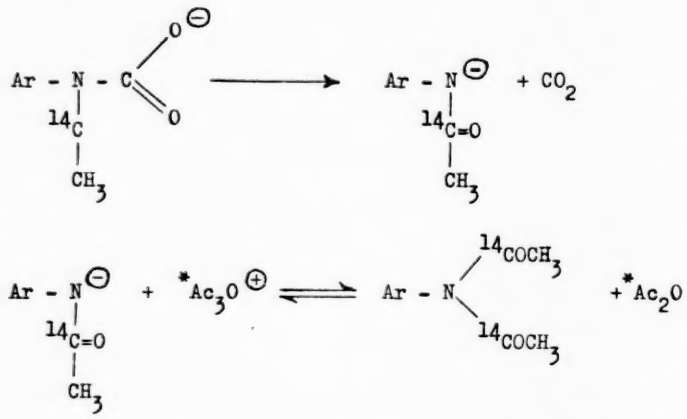


or

II



[6] E.A.Evans, J.L.Huston and T.M.Norris, J.Amer.Chem.Soc. 74, 4985 (1952).



When ethyl isocyanate is applied, the molar activity of the N-ethyl-diacetamide obtained is essentially less than that of the acetic anhydride. The investigation of the reaction with other alkylisocyanates is in course.

Tetrahedron Letters No. 2, pp. 19-22, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

INVESTIGATION OF THE PYROLYTIC DECARBOXYLATION OF CARBOXYLIC ACIDS WITH ^{14}C

MECHANISM OF THE FORMATION OF CAMPHOR FROM HOMOCAMPHORIC ACID

L.Ötvös and L.Noszkó

Central Research Institute for Chemistry of the Hungarian Academy of Sciences

(Received 15 December 1959)

THE oldest, but in many cases still practically used method to prepare ketones is based on the dry distillation of a salt of the respective carboxylic acid. Numerous conceptions have been proposed[1-5] with regard to the mechanism of the reaction. The most feasible suggestion seemed to be that of Nuenhoeffer and Paschke[2] according to which the reaction is taking place through a β-keto-carboxylic acid arising from a condensation process. According to Lee and Spinks[5] the most contestable point of this assumption is the fact that no explanation can be given in this way for the formation of diaryl ketones. In our opinion the reaction may be treated on a more uniform basis, if the formation of the respective alkyl cation is

---

[1] E.Bamberger, Ber.Dtsch.Chem.Ges. 48, 3517 (1910).

[2] O.Neunhoeffer and P.Paschke, Ber.Dtsch.Chem.Ges. 72, 919 (1939)

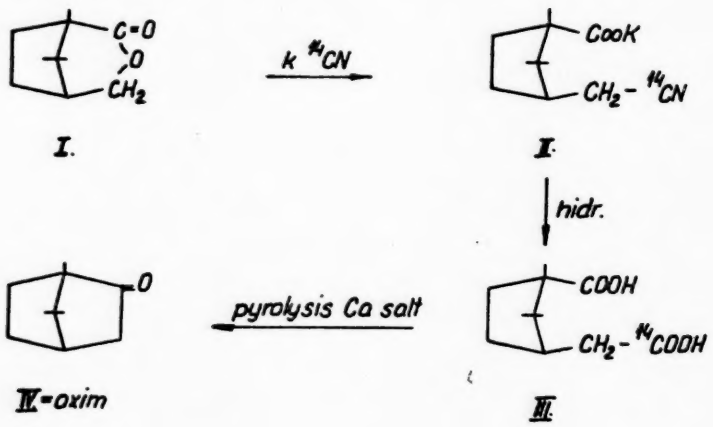
[3] A.L.Miller, N.C.Cook and F.C.Whitmore, J.Amer.Chem.Soc. 72, 2732 (1950).

[4] J.Bell and R.I.Reed, J.Chem.Soc. 1383 (1952)

[5] C.C.Lee and J.W.T.Spinks, J.Org.Chem. 18, 1079 (1953)

assumed to be the first step which is followed by a decarboxylation of the S_E2 type. Among the results of Lee and Spinks experiments, carried out with ^{14}C, the soundness of the data referring to the pyrolysis of calcium-1-^{14}C-acetate + calcium-phenylacetate given in full details has been disputed by Nefedov, Toropova and Skulski[6] on the basis of their own experiments with isotopes.

In order to test the mechanism assumed by Neunhoeffer and Paschke, our choice fell on a model in which one of the carbon atoms adjacent to a carboxyl group was a quarternary while the other a secondary one. In order to obtain a satisfactory isolability of the mixed ketone arising both carboxyl groups were built into the same molecule, and the origin of the emerging CO_2 has been determined by indication with ^{14}C. Accordingly the pyrolysis of the Ca-salt of homocamphoric acid, containing ^{14}C-carboxyl, adjacent to the secondary carbon atom, has been investigated The preparation of the compound was carried out as follows: the lacton



[6] V.D.Nefedov, M.A.Toropova and I.A.Skulskij, Zs.Fiz.Him. 29, 2236 (1955)

ring of α-campholide (I), prepared according to Komppa,[7] was opened with $K^{14}CN$, then the obtained potassium salt of homocamphoric acid semi-nitrile (II) was subjected to acidic hydrolysis and transformed into the Ca-salt. Dry distillation of the product gives camphor (IV) which could be identified in form of its oxime. The scheme of preparation is given in the figure on page 20, the values of the activities in Table 1. The determination of the latter was carried out with a gas phase counter.

TABLE 1

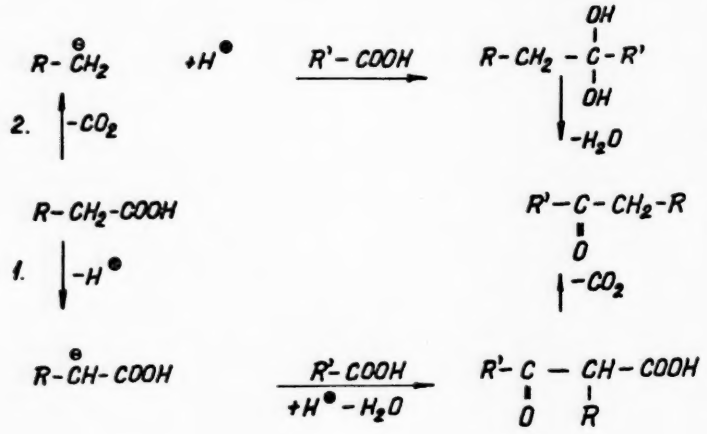
Compound	Activity, μc/mM
II	17.2
III	17.2
IV-oxim	0.19

The results show clearly that in the course of the pyrolysis the activity passes entirely into the liberated CO_2. Even if steric factors, or the difference in the bonding energies of the carboxyl groups or in their tendency to produce acyl cations are taken into consideration, these cannot provide for such a significant difference in the behaviour of the two groups. The reaction, however, may be explained if we assume that, by the addition of the CH_2-group, attached to the carboxyl-group marked with ^{14}C, 3-carboxy-camphor is intermediately formed which then suffers

[7] G.Komppa, Ber.Dtsch.Chem.Ges. 41, 4470 (1903)

decarboxylation under the conditions of the reaction. This means essentially the verification of the condensation mechanism in the case of our model.

We are of the opinion that in a general sense also this reaction may be considered as an anionic addition process. The formation of the carbanion may take place in two different ways: by splitting off of a proton, or else by the catalysed liberation of CO_2. In the former case the reaction will occur through a β-keto-carboxylic acid, in the latter through the alcoholate of a geminal diol.



Where a possibility for both reaction directions is given, the β-keto-carboxylic-acid mechanism will dominate, as shown by the experimental results of Lee and Spinks as well as of Nefedov, Toropova and Skluski. If there is no possibility to split off the proton, the reaction occurs by the other mechanism. Investigations are in course in this direction, with aromatic substituted carboxylic acids.

Tetrahedron Letters No. 2 pp. 23-27, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

PORPHYRIN NUCLEAR MAGNETIC RESONANCE SPECTRA*

J. Ellis, A.H. Jackson, G.W. Kenner and J. Lee**

University of Liverpool

(Received 14 December 1959, in revised form 7 January 1960)

THE nuclear magnetic resonance spectra[2] of porphyrins show a number of uncommon features, of which the most noteworthy is a peak at very high field. The spectrum of aetioporphyrin I*** in trifluoroacetic acid (TFA) is shown in the figure; in this strongly acidic medium the porphyrin is

---

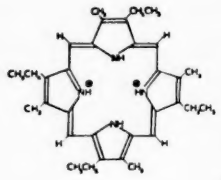
* Some of the results recorded in this paper were presented at the XVLLth International Congress of Pure and Applied Chemistry (Section on Natural Pigments and their Biogenesis) in Munich, September, 1959. Spectra of several porphyrin esters in deuterochloroform solution have been described recently;[1] the published interpretation of these results agrees with this communication.

** Present address: Department of Chemistry, Manchester College of Science and Technology.

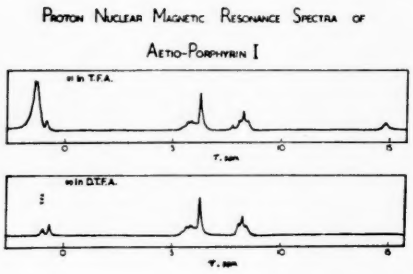
*** 1:3:5:7- Tetramethyl-2:4:6:8-tetraethylporphin.

1 E.D. Becker and R.B. Bradley, J.Chem.Phys. In press; we thank Dr. Becker for sending us his manuscript.

2 A Varian V-4300-B 40.00 Mc/sec spectrometer was employed, together with a sample spinner, field stabiliser and Varian recorder. Tetramethyl silane was used as an internal reference, and spectra were calibrated by the side-band method.



I



presumably present as the di-cation (I) in which all four nitrogen atoms are protonated[3]. We assign the high-field peak at 1ϒ.89[4] to the NH protons, because this peak is absent from the spectrum of aetioporphyrin I in deuterotrifluoroacetic acid (DTFA) (in which one would expect the NH protons to be exchanged for deuterium). [In TFA, ϒ-phylloporphyrin XV* shows three

---

* 1:3:5:8:ϒ-Pentamethyl-2:4-diethyl-7-carboxyethylporphin

3 A.Neuberger and J.J. Scott, Proc.Roy.Soc. A 213, 307 (1952)

4 Numerical values of the chemical shifts recorded in this paper are in parts per million, and are referred to the τ-scale, on which the tetramethylsilane peak is taken as +10.00 by definition (see G.V.D. Tiers, J.Phys.Chem. 62, 1151 (1958)

peaks in the high field region at 13.64(1), 13.84(1), 14.43(2) (the figures in parentheses indicate relative integrated intensities); these may arise from the non-equivalence of the NH groups.]

The peak at 6.30, the quadruplet centred at 5.80, and the triplet at 8.22 are clearly due to the ring-methyl, ring methylene, and side-chain methyl group resonances respectively, although they are shifted slightly from the normal positions. The low-field peak in DTFA solution at -0.69 (present in TFA at -0.88 on the edge of the solvent band) must therefore be due to the methine protons; the neighbouring peak at -0.97 shows the TFA produced by exchange of the NH protons as well as a trace in the DTFA. On the other hand there is no obvious explanation for the peak at 7.73, although it must be connected in some way with the presence of TFA, (see below).

These assignments have been confirmed with other porphyrins. For example, the spectrum of octamethyl porphin in TFA shows peaks at -0.71 (methine), 6.2 (methyl), 7.77 and 14.90 (NH); the peaks at 7.77 and 14.90 are both absent from the spectrum in DTFA.

Simple porphyrins, (especially octamethylporphin) are not sufficiently soluble for their spectra to be measured in chloroform, whilst concentrated sulphuric acid solutions are too viscous and too dilute to give good spectra. On the other hand the esters of the more complex porphyrins are often sufficiently soluble for good spectra to be obtained in chloroform, as well as in TFA and DTFA. Thus the spectra of both the free porphyrin ester and the salts of the corresponding acids can be obtained. The behaviour of coproporphyrin III methyl ester* when dissolved in chloroform

* 1:3:5:8-Tetramethyl-2:4:6:7-tetracarboxyethylporphin tetramethyl ester.

and in DTFA shows an interesting contrast; in the former case the methine peak is at 0.04, in the latter at -0.82. This effect of the additional central protons recalls the effect of electronegative substituents in aromatic compounds.[5]

A fairly sharp high-field peak at 13.89 has been observed for coproporphyrin I methyl ester* in deuterochloroform, but with chloroform solutions we find broad high-field bands doubtless caused by intermediate rates of ^{14}N quadrupolar relaxation. Solvent-solute chemical exchange is presumably responsible for the sharper peaks in TFA solutions.

The band at 7.7-7.8, present in the spectra of all TFA solutions of porphyrins, is absent from spectra taken in either DTFA or chloroform solutions; it thus apparently arises from the presence of TFA although its precise origin remains uncertain.

The unexpected positions of the low-field peak (due to the methine protons) at 5.5 p.p.m. lower than ethylene and the very high field peak (NH protons, 12 p.p.m. high than pyrrole NH[6]) can be attributed on theoretical grounds to the effect of ring currents[7] in the large conjugated porphyrin ring system, whereby the NH protons are much more highly shielded than the NH proton of pyrrole, and the methine protons less

---

* 1:3:5:7-Tetramethyl-2:4:6:8-tetracarboxyethlporphin tetramethyl ester.

5 J.A.Pople, W.G.Schneider and H.J.Berstein, High Resolution Nuclear Magnetic Resonance pp. 258 ff. McGraw-Hill, New York (1959).

6 R.J. Abraham and H.J.Bers+ein, Canad.J.Chem. 37, 1056 (1959).

7 J.A.Pople, W.G.Schneider and H.J.Bernstein, High Resolution Nuclear Magnetic Resonance pp. 180,251. McGraw-Hill, New York (1959).

shielded than those of ethylene. It has been reported[1] that the magnetic ring model[8] can account semi-quantitatively for the methine peak, but the calculated position of the NH peak is then far too high. Our own calculations (with 1.28 Å current loop spacing) agree; for example, an assumed ring of 18 electrons with a radius of 3.0 Å locates the methine peak at -1.2, but the NH peak is then at 29.3. In order to fit these calculations to the observations it is necessary to assume an effective number of 9.4 free electrons in a ring of radius 3.7 Å.

---

[8] C.E. Johnson and F.A. Bovey, J.Chem.Phys. 29, 1012 (1958).

Tetrahedron Letters No. 2, pp. 28-30, 1960. Pergamon Press Ltd. Printed in Great Britain.

THE DEUTERIUM ISOTOPE EFFECT IN THE PERMANGANATE OXIDATION OF AROMATIC TRIFLUOROMETHYL ALCOHOLS

R. Stewart and R. Van der Linden

Department of Chemistry, University of British Columbia, Vancouver

(Received 21 December 1959)

PHENYL trifluoromethyl carbinols are oxidized by aqueous alkaline permanganate to the corresponding ketones. We wish to report a kinetic isotope effect of unusual size for the reaction of the 1-deuterio analogs of these compounds.

$$YC_6H_4CDOHCF_3 + 2MnO_4^- + 2OH^- \longrightarrow YC_6H_4COCF_3 + 2MnO_4^= + H_2O + HDO$$

1-Phenyl-2,2,2-trifluoroethan-1-ol (I) and its p-methyl (II) and m-bromo (III) derivatives were prepared by $LiAlH_4$ reduction of the corresponding ketones. (II), b.p., 94.5 (12 mm) $n_D^{24} = 1.4650$. Found: C, 57.1; H, 5.0. $C_9H_9F_3O$ requires C, 56.9; H, 4.7. Phenylurethan of (II), m.p., 104-105. Found: C, 62.1; H, 4.5; N, 5.1. $C_{16}H_{14}F_3O_2N$ requires C, 62.1; H, 4.5; N, 5.1. (III), b.p. 115 (12 mm), $n_D^{27} = 1.5005$. Found: C, 38.0; H, 2.5; Br, 31.6. $C_8H_6F_3BrO$ requires C, 37.1; H, 2.4; Br, 31.4.

p-Tolyl trifluoromethyl ketone[1] was prepared from p-tolyl magnesium bromide and trifluoroacetic acid. Bromination of phenyl trifluoromethyl

---

[1] J.D. Park, H.A. Brown and J.R. Tacker, J.Amer.Chem.Soc. 73, 709 (1951)

ketone gave the m-bromo derivative, b.p., 83.5 (12 mm), n_D^{24} = 1.5030. Found: C, 38.2; H, 1.6; F, 20.6. $C_8H_9OF_3Br$ requires C, 38.0; H, 1.5; F, 22.5. 2,4-Dinitrophenylhydrazone, m.p. 121.5-123. Found: C, 38.8; H, 2.5; N, 12.0; F, 12.0. $C_{14}H_8O_4N_4F_3Br$ requires C, 38.6; H, 1.9; N, 12.9; F, 13.2.

1960

1-Phenyl-2,2,2-trifluoroethan-1-ol-1-d and its p-methyl and m-bromo derivatives were prepared by $LiAlD_4$ reduction. The infrared spectra of these compounds were identical with those of their protio analogs, I, II and III, except for the shift of the C-H stretching band from 2895 cm^{-1} to 2150 cm^{-1}.

The purity of the alcohols was checked by vapour phase chromatography and samples for reaction were collected in several cases by this means. The reaction was followed as previously described[2]. The oxidation in aqueous solution follows the rate law

$$V = k\,[ArCHOHCF_3][MnO_4^-][OH^-]$$

for both the protio and deuterio compounds with the following rates.

Permanganate oxidation rates in 0.2 M NaOH at 25

	k_H $l.mole^{-1}sec^{-1}$		k_D $l.mole^{-1}sec^{-1}$	$\frac{k_H}{k_D}$
$C_6H_5CHOHCF_3$	7.5	$C_6H_5CDOHCF_3$	0.47	16.0
$p\text{-}CH_3C_6H_4CHOHCF_3$	8.4	$p\text{-}CH_3C_6H_4CDOHCF_3$	0.52	16.1
$m\text{-}BrC_6H_4CHOHCF_3$	7.6	$m\text{-}BrC_6H_4CDOHCF_3$	0.47	16.2

[2] R. Stewart, J.Amer.Chem.Soc. 79, 3057 (1957)

The magnitude of the isotope effect[3] can be explained on either of the following grounds. Either the reaction is a complex one involving consecutive dependent steps such that the overall isotope effect is a cumulative one or the reaction is occurring with loss of the bending modes of the carbon-hydrogen bond in the transition state in addition to the loss of the stretching mode.

The acidity of these alcohols (pK_a = 11.9, 12.0 and 11.5 for I, II and III) is such that they exist largely as their anions under the oxidation conditions. A transfer of hydride ion from the alkoxide ion to Mn(VII), favoured for the analogous benzhydrol system,[2] is difficult to reconcile with the relative indifference of the reaction rate to nuclear substitution. A more complete discussion of the mechanism will be published later.

---

[3] K.B. Wiberg, Chem.Rev. 55, 713 (1955).

Tetrahedron Letters No. 2, pp. 31-35, 1960. Pergamon Press Ltd. Printed in Great Britain.

RACEMIZATION AND RADIO-CHLORIDE EXCHANGE OF P-CHLOROBENZHYDRYL CHLORIDE IN ACETONE[1]

S. Winstein and John S. Gall

Dept. of Chemistry, University of California, Los Angeles, Calif.

(Received 2 January 1960)

In rearrangement, exchange and solvolysis reactions of neutral organic substrates proceeding by way of carbonium ions, it is important to distinguish between ionization and dissociation and to consider explicitly the role of different ionic intermediates representing various stages of ionization-dissociation[2,3]. In fact, a considerable body of information is now available on the intimate course of carbonium ion reactions of allylic, homoallylic and various other rearranging systems[2,3]. We have now compared the rates of racemization and radio-chloride exchange of p-chlorobenzhydryl chloride in acetone solvent. These differ by a substantial factor and therefore give considerable insight into the behavior of the ionic intermediates involved.

---

[1] Research supported by the National Science Foundation.

[2] (a) W. G. Young, S. Winstein and H. L. Goering, J. Am. Chem. Soc. 73, 1958 (1951); (b) S. Winstein, et.al., ibid. 74, 1154, 2165, 2171 (1952); (c) C. A. Grob and S. Winstein, Helv. Chim. Acta 35, 782 (1952).

[3] (a) S. Winstein, et.al., J. Am. Chem. Soc. 76, 2597 (1954); Chemistry and Industry, 664 (1954); J. Am. Chem. Soc. 78, 328, 2763, 2767, 2784 (1956); 80, 169, 459 (1958); (b) S. Winstein, Experientia Supplementum II 137 (1955); (c) E. F. Jenny and S. Winstein, Helv. Chim. Acta 41, 807 (1958).

Treatment of optically active p-chlorobenzhydrol[4], m.p. 53-55°, $[\alpha]_D^{25}$ +18.2° (Me_2CO,C=13), with thionyl chloride in benzene gives rise to p-chlorobenzhydryl chloride, $[\alpha]_D^{25}$ -3.4° (Me_2CO,C=10), with a low rotation which is sufficiently high, however, to permit measurement of first order racemization rates with an accuracy of ca. 5 percent.

As summarized in Table I, p-chlorobenzhydryl chloride racemizes with first order kinetics at a convenient rate in acetone at 75°C. The first order racemization rate constant, k_α, is increased slightly by added lithium chloride or perchlorate and enormously by tetrabutylammonium chloride or perchlorate. The first order rate constants[5] for exchange with lithium or tetrabutylammonium radio-chloride, symbolized by k_e, are considerably smaller than the polarimetric rate constants. The k_e and k_α values show a roughly linear[3a] pattern of increase with salt concentration, (MY), and they may be fit quite well by equations (1) and (2), respectively, as summarized in Table II.

$$k_e = b_e\,(MCl) \qquad (1)$$

$$k_\alpha = k_\alpha^\circ\,[1 + b_\alpha\,(MY)] \qquad (2)$$

The relative efficiency of perchlorate salts compared to the corresponding chlorides in promoting racemization and the observed (k_α/k_e) ratios of ca. 15 in the presence of chloride salts show that ionization is the main cause of racemization. More direct so-called S_N2 displacement by added chloride is relatively unimportant, as can be shown analytically with

---

[4] J. Kenyon and G. H. Green, J. Chem. Soc. 751 (1950).

[5] e.g., L. J. leRoux and E. R. Swart, ibid. 1475 (1955).

1960

Table I

Summary of Racemization and Radio-Chloride Exchange Rates in Acetone at 75.0°C

[RCl] 10^2M	Added Salt	10^2 M	10^5k Values (sec $^{-1}$)		
			10^5k_a	10^5k_e	(k_a/k_e)
17.2[a]			1.29		
16.0[a]	LiCl	0.55[b]	1.74	0.101	17
16.4[a]	LiCl	1.10[b]	2.16	.169	13
12.1[a]	$LiClO_4$	4.00	7.37		
16.9[a]	Bu_4NClO_4	4.00	54.4		
1.07	Bu_4NCl	0.623[b]		1.05	
12.1[a]	Bu_4NCl	.900	22.6		16
1.04	Bu_4NCl	1.71[b]		2.75	
1.10	Bu_4NCl	1.79[b]		2.83	
1.16	Bu_4NCl	2.60[b]		4.11	
19.1[a]	Bu_4NCl	2.70	65.4		15
20.0[a]	Bu_4NCl	4.65[b]	107.0	7.39	15
1.07	Bu_4NCl	4.84[b]		7.45	

[a] Optically active chloride

[b] Radio-chloride

the aid of equations (3), (4) and (5). In these equations, k_1 and k_2 are

$$k_e = k_1E + k_2 \qquad (3)$$

$$k_a = k_1R + 2k_2 \qquad (4)$$

Table II

Fit of k_e and k_a Values to Equations (1) and (2)

Salt	$10^5 k^\circ$ (sec^{-1})	b	Ave. Fit % of k
Racemization			
LiCl	1.29	62	0.6
$LiClO_4$	1.29	118[a]	-
Bu_4NClO_4	1.29	1030[a]	-
Bu_4NCl	1.29	1780	2.2
Exchange			
LiCl	0	1.6×10^{-4}	8.5
Bu_4NCl	0	1.6×10^{-3}	2.7

[a] Based on only one salt concentration

$$\frac{k_e}{k_a} = \frac{(E/R) + (k_2/k_1R)}{1 + 2(k_2/k_1R)} \qquad (5)$$

first order rate constants for ionization and S_N2 displacement, respectively, R is the fraction of all the ionic intermediates from ionization of chlorobenzhydryl chloride which lose stereochemical configuration and become racemic, and E is the fraction of all such ionic intermediates which lead to chloride exchange. By setting (E/R) equal to zero an upper limit to the ratio $[k_2/(k_1R)]$ of $[(k_e/k_a) / (1 - 2\,k_e/k_a)]$ may be set. On this basis, no more than ca. 13 percent of the racemization of p-chlorobenzhydryl chloride in the presence of chloride salt can be due to direct chloride displacement.

The b_a values in Table II reflect considerable specificity as regards the nature of the added salt, and they become very large for tetrabutylammonium chloride and perchlorate. Since racemization proceeds largely through ionization, the b_a values show that salt effects on ionization of chlorobenzhydryl chloride can be very large in acetone[6].

Setting (k_2/k_1R) equal to zero in equation (5) gives an upper limit of (k_e/k_a) or 1/15 for the ratio (E/R). Therefore, less than one-fifteenth as big a fraction of ionic intermediates from ionization of chlorobenzhydryl chloride lead to exchange as become racemic. Since the maximum value of R is unity, the maximum value of E is 0.07. Chloride exchange is inevitable if dissociated carbonium ions are formed and returned to covalent chloride[3a]; therefore, the maximum fraction of ionic intermediates which become dissociated before return to the covalent condition is also 0.07.

The above analysis shows that at least 93 percent of carbonium ion intermediates from ionization of chlorobenzhydryl chloride return to the covalent condition before dissociating. Since at least some of the ionic intermediates may be expected to maintain configuration and make R less than unity, the fraction of intermediates which become covalent before dissociating may be even greater.

In acetic acid solvent[2,3], rate of solvolysis (k_t), as well as racemization and radio-chloride exchange, can be measured. In this solvent, k_a exceeds both k_e and k_t by factors[7] considerably larger than the (k_a/k_e) ratios observed in acetone.

---

[6] S. Winstein, S. Smith and D. Darwish, J. Am. Chem. Soc. 81, 5511 (1959); Tetrahedron Letters 16, 24 (1959).

[7] J. S. Gall, unpublished work.

1960

Tetrahedron Letters No.3, pp 1-8, 1960. Pergamon Press Ltd, Printed in Great Britain.

THE STRUCTURE OF METAGENIN

Ken'ichi Takeda and Kaname Hamamoto

Research Laboratory, Shionogi & Co., Ltd., Osaka, Japan

(Received 1st January 1960)

PREVIOUSLY, 25D,5β-spirostane-2β,3β,x-triol was proposed by us[1] as the structure of metagenin, a sapogenin isolated from Metanarthecium luteo-viride Maxim., and it was also reported that the position of the unknown hydroxyl group in metagenin was limited to C-6, C-7 or C-11. We have now completely established the structure of this sapogenin to be 25D,5β-spirostane-2β,3β,11α-triol (I) from the following experimental results.

Samogenin from Metagenin

Metagenin acetonide (Ia), obtained in the usual manner as described earlier,[1] was converted to metagenone (II), m.p. 248°,* $[\alpha]_D^{25}$ - 4.0°, I.R. λ_{max}^{Nujol} 2.95μ (hydroxyl) and 5.88μ (ketone), by CrO_3-pyridine oxidation followed by dilute acetic acid hydrolysis. Metagenone gave a diacetate (IIa), m.p. 240-242°, and this diacetate again gave the unchanged parent ketone (II) by the action of alkali.

Although metagenone diacetate underwent the Huang-Minlon reduction[2] and

---

[1] K. Takeda, T. Okanishi, K. Hamamoto, A. Shimaoka and N. Maezono, Yakugaku Zassi 77, 175 (1957).

* M.p. not corrected.

[2] Huang-Minlon, J. Amer. Chem. Soc. 68, 2487 (1946).

afforded samogenin diacetate (III),[3,4] m.p. 197-198°, in ca.25% yield when the reaction mixture was acetylated by acetic anhydride, metagenone gave neither a semicarbazone nor a hydrazone under the usual conditions.

From these results, it was confirmed that the two vicinal hydroxyl groups are located at C-2 and C-3, that both are β-oriented, and that the A/B ring juncture is cis. Furthermore, the position of the keto group in metagenone at C-6 is excluded by the stability of the substance to alkali.

Reduction of Metagenone

$NaBH_4$ reduction of metagenone afforded a new triol (IV), m.p. 134-136°, $[\alpha]_D^{25}$ - 47,3°, I.R. λ_{max}^{Nujol} 2.93 and 3.01μ (hydroxyl), epi-metagenin, while with Na and isopropyl alcohol it afforded metagenin. In the case of $LiAlH_4$ reduction of diacetyl metagenone, it gave epi-metagenin as a main product together with a small amount of metagenin. epi-Metagenin gave only a diacetate (IVa), m.p. 175°, I.R. λ_{max}^{Nujol} 2.85μ (hydroxyl), 7.88, 7.93 and 8.18μ (acetate), by the action of acetic anhydride-pyridine at room temperature and epi-metagenin acetonide (IVb), m.p. 218-221°, was not affected by cathylation.[5] On the other hand, metagenin acetonide (Ia) readily gave a cathylate (Ic), m.p. 159°, and it also gave an acetonide acetate (Ib), m.p. 202-204°, under very mild conditions. These findings indicate that the third hydroxyl group in metagenin and its epimeric one in epi-metagenin has an equatorial and an axial conformation, respectively.

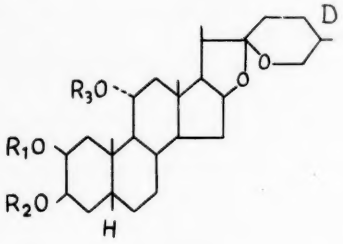
---

[3] C. Djerassi and J. Fishman, J. Amer. Chem. Soc. 77, 4291 (1955).

[4] The authors are indebted to Dr. C. Djerassi for his kind donation of the valuable sample of samogenin diacetate.

[5] L. F. Fieser, J. E. Herz, M. W. Klohs, M. A. Romers and T. J. Utne, J. Amer. Chem. Soc. 74, 3309 (1952).

1960



I $R_1=R_2=R_3=H$ Metagenin

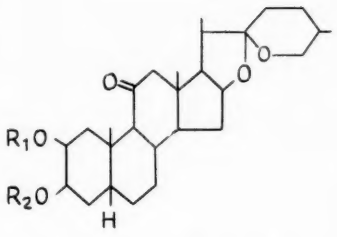
Ia $\begin{matrix}R_1\\R_2\end{matrix}\!\!>\!=\!<C<\begin{matrix}CH_3\\CH_3\end{matrix}$ $R_3=H$

Ib $\begin{matrix}R_1\\R_2\end{matrix}\!\!>\!=\!<C<\begin{matrix}CH_3\\CH_3\end{matrix}$ $R_3=Ac$

Ic $\begin{matrix}R_1\\R_2\end{matrix}\!\!>\!=\!<C<\begin{matrix}CH_3\\CH_3\end{matrix}$ $R_3=C_2H_5OCO$

Id $R_1=R_2=H$ $R_3=Ac$

Ie $R_1=R_2=Ms$ $R_3=Ac$

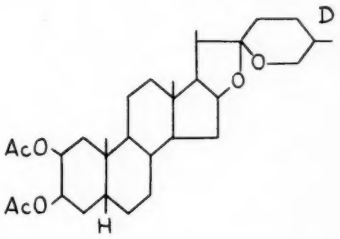


II $R_1=R_2=H$ Metagenone

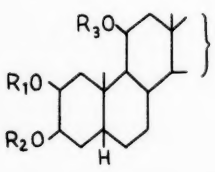
IIa $R_1=R_2=Ac$

IIb $\begin{matrix}R_1\\R_2\end{matrix}\!\!>\!=\!<C<\begin{matrix}CH_3\\CH_3\end{matrix}$

IIc $R_1=R_2=Ms$



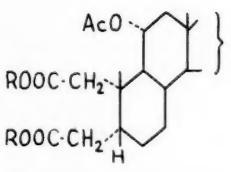
III Samogenin Diacetate



IV $R_1=R_2=R_3=H$ epi-Metagenin

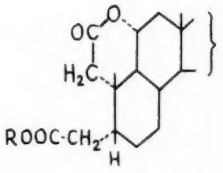
IVa $R_1=R_2=Ac$ $R_3=H$

IVb $\begin{matrix}R_1\\R_2\end{matrix}\!\!>\!=\!<C<\begin{matrix}CH_3\\CH_3\end{matrix}$ $R_3=H$



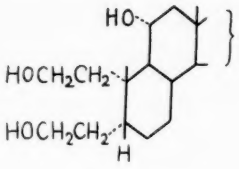
V R=H

Va $R=CH_3$

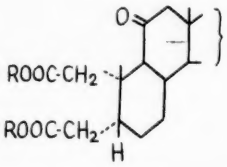


VI R=H δ-Lactone

VIa $R=CH_3$

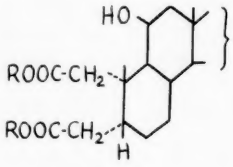


VII



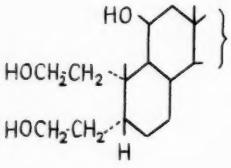
VIII R=H Metagenic Acid

VIIIa R=CH_3

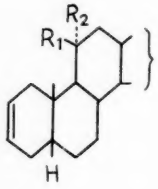


IX R=H

IXa R=CH_3

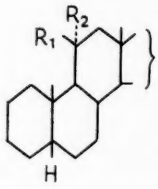


X



XIa R_1=H R_2=OAc

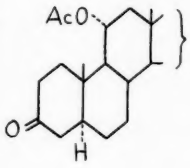
XIb R_1, R_2 >=O



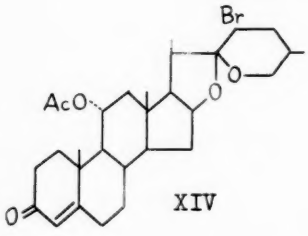
XII R_1=H R_2=OH

XIIa R_1=H R_2=OAc

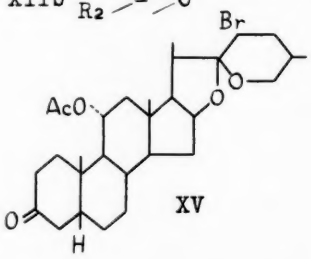
XIIb R_1, R_2 >=O



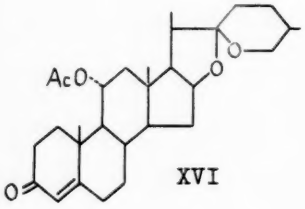
XIII



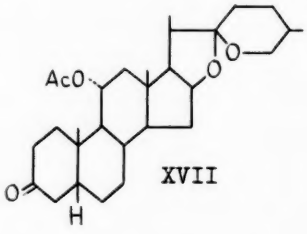
XIV



XV



XVI



XVII

1960

Formation of δ-Lactone

CrO_3 oxidation of the x-monoacetyl derivative (Id), m.p. 219°, which was obtained from metagenin acetonide acetate (Ib) by the action of dilute acetic acid, gave an acetoxy A-seco acid (V), m.p. 282° (decomp.), $[\alpha]_D^{20}$ - 67,6°, (dimethyl ester (Va), m.p. 98-100°), and this seco acid readily afforded a δ-lactone (VI), m.p. 248°, $[\alpha]_D^{20}$ - 53,4°, I.R. λ_{max}^{Nujol} 5.75 (δ-lactone) and 5.81 μ (carboxylic acid), (methyl ester (VIa), m.p. 172°), by saponification with acid or alkali. The same δ-lactone was also obtained from dimethyl metagenate (VIIIa)[1] when treated with Na and isopropyl alcohol or directly from metagenin itself with CrO_3 in acetic acid at 15° as a by-product of metagenic acid (VIII). This lactone afforded a triol (VII), m.p. 208°, with $LiAlH_4$. On the other hand, another hydroxy A-seco acid (IX), m.p. 222° (decomp.), I.R. λ_{max}^{Nujol} 2.78 (hydroxyl), 5.88 and 5.93 μ (carboxylic acid), (dimethyl ester (IXa), m.p. 163°), was obtained by $NaBH_4$ reduction of dimethyl metagenate (VIIIa). This hydroxy A-seco acid resisted lactone formation and its dimethyl ester was oxidized back to the parent dimethyl metagenate. The hydroxyl group of this seco acid was not affected by mild acetylation. This acid gave a triol (X), m.p. 216-217°, different from the above-mentioned triol (VII).

From these results it is clear that the unknown hydroxyl group in metagenin is located on the same side as the acetic acid residue of samogenic acid, in other words, this hydroxyl group must be α-oriented. Furthermore, as this hydroxyl group has an equatorial conformation, C-11 is the most probable position for this group. Comparison of the molecular rotation values of the corresponding metagenin and epi-metagenin derivatives also support this assignment (cf. Table 1).[6] However

---

[6] L.F. Fieser and M. Fieser, Steroids p. 179 Reinhold, New York (1959).

there remain some doubtful points in this assumption from the following facts: (i) metagenone acetate was affected by the Huang-Minlon reduction and afforded samogenin as described above; (ii) the rotatory dispersion curve of metagenone (peak at $[\alpha]_{330}$ + 112°, trough at $[\alpha]_{262.5}$ - 720°) is almost identical with that of 7-keto cholanic acid derivatives,[7,8] although this could also be compatible with an 11-keto sapogenin[9] because of the strong negative background rotation[9] of the spiroketal side chain.

Table 1. Molecular Rotation Values of Metagenin and Epi-metagenin Derivatives

	Sapogenin		Diacetate		Acetonide	
	$[\alpha]_D$	M_D	$[\alpha]_D$	M_D	$[\alpha]_D$	M_D
Metagenin (A)	-82°	-368°	-67°	-359°	-86°	-419°
epi-Metagenin (B)	-47°	-212°	-50°	-264°	-56°	-272°
M_D (B) - M_D (A)	+156°		+95°		+147°	

Elimination Reaction of the Vicinal Hydroxyl Groups in Metagenin and the Synthesis of 11α-Hydroxy-25D,5β-spirostane

For further confirmation we next examined the elimination reaction of the vicinal two hydroxyl groups in metagenin by the method of C. Djerassi and J. Fishman.[3] 2,3-Dimesyloxy-x-acetyl-metagenin (Ie), m.p. 225° (decomp.),

---

[7] C. Djerassi and W. Closson, J. Amer. Chem. Soc. 78, 3761 (1956).

[8] The rotatory dispersion curve of metagenone was kindly measured by Dr. C. Djerassi of Stanford University.

[9] C. Djerassi and R. Ehrlich, J. Amer. Chem. Soc, 78, 440 (1956).

obtained from the x-monoacetate (Id) by the usual manner, was converted into the Δ^2-derivative (XIa), m.p. 165°, with NaI in acetone and this was reduced catalytically to the saturated monoacetoxy derivative (XIIa), m.p. 187-188° (free alcohol (XII), m.p. 182,5-183°, $[\alpha]_D^{25}$ - 77°). A similar reaction was carried out on metagenone and the ketone (XIIb), m.p. 172-173°, $[\alpha]_D^{25}$ - 48°, was obtained through IIc, m.p. 208° (decomp.), and XIb, m.p. 178°. This ketone also gave the above-mentioned monohydroxy sapogenin (XII) with Na and isopropyl alcohol but was resistant to Huang-Minlon reduction.

Finally, 11α-hydroxy-25D,5β-spirostane or its acetate was synthesized from 11α-acetoxy-tigogenone (XIII).[10,11] The introduction of the double bond at C-4 was carried out by the method reported by J. Romo,[11] but the bromine atom at C-23 was eliminated after saturation of the double bond,[12] since XIV[13] (free alcohol, m.p. 197°, decomp.) was rather resistant to debromination and the yield of XVI was very low. The Huang-Minlon reduction of the saturated acetoxy ketone (XVII), m.p. 205-207°, afforded the anticipated 11α-hydroxy derivative, and the latter was also obtained directly from XV by the same reaction with simultaneous debromination. The resulting 11α-hydroxy-25D,5β-spirostane or its acetate was identical in all respects with the corresponding degradation product of metagenin.

---

[10] J. H. Chapman, J. Elks, G. H. Phillips and L. J. Wyman, J. Chem. Soc. 1956, 4344.

[11] J. Romo, C.A. 50, 12088 (1956); Bol. inst. quim. U.N.A.M. 7, 53 (1955).

[12] O. Mancera, H. J. Ringold, C. Djerassi, G. Rosenkranz and F. Sondheimer, J. Amer. Chem. Soc. 75, 1286 (1953).

[13] Attempts to crystallize the acetate (XIV) were unsuccessful.

This is the first example of an 11-oxygenated steroidal sapogenin isolated from a plant source. A more detailed report of this work will be published in due course in the Chem. Pharm. Bull.

Tetrahedron Letters No. 3, pp. 9-12, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

THE IDENTITY OF JATAMANSONE AND VALERANONE

J.Křepinský, V.Herout and F.Šorm

Department of Natural Products, Institute of Chemistry,

Czechoslovak Academy of Science, Prague

(Received 8 January 1960)

THE preliminary results, published by Govindachari et al.,[1,2] enabled us to prove the identity of the so called jatamansone from Nardostachys jatamansi (Valerianaceae) with valeranone from Valeriana officiualis L., the isolation of which was carried out by Stoll et al.[3,4] and by us.[5] The identity of both compounds in question follows from the comparison of both the physical constants of derivatives (Table 1) and of the physical constants of degradation products which were prepared independently in this Laboratory in a manner which differed from the procedure of the Indian authors in details only (Table 2).

---

[1] T.R. Govindachari, S.Rajadurai and B.R. Pai, Chem. Ber. 91, 908 (1958).

[2] T.R. Govindachari, B.R.Pai, K.K. Purushothaman and S. Rajadurai, Tetrahedron Letters No.15, 5 (1959).

[3] A.Stoll, E.Seebeck and D. Stauffacher, Schweiz. Apoth.-Ztg. 95, 115 (1957).

[4] A.Stoll, E.Seebeck and D. Stauffacher, Helv. Chim. Acta. 40, 1205 (1957).

[5] J.Křepinský, V.Herout and F.Šorm, Chem. listy 52, 1784 (1958); Coll. Czech. Chem. Comm. 24, 1884 (1959).

On treatment with lithium aluminium hydride, valeranone afforded the alcohol valeranol $C_{15}H_{28}O$ (d_4^{20} 1.0046, n_D^{20} 1.5005, $[\alpha]_D^{20}$ + 51.4°, chloroform) which on dehydration with phtalic anhydride at 270 - 280° yielded unsaturated hydrocarbon valerene $C_{15}H_{26}$ (d_4^{22} 0.9045, $[\alpha]_D^{22}$ + 96.07°). The latter, on hydrogenation with PtO_2 (Adams) afforded the saturated hydrocarbon valerane of molecular formula $C_{15}H_{28}$ (d_4^{20} 0.8965, n_D^{20} 1.4830). The same hydrocarbon was obtained from valeranone ethylene thioketal on treatment with Raney-nickel in dioxan. Both compounds were proved identical by comparison of infra-red spectra and physical constants; the infra-red spectrum of valerane, however, was unlike the spectra of all hitherto known saturated bicyclic sesquiterpenes.[6]

TABLE 1.

Comparison of physical constants

Valeranone		Jatamansone	
d_4^{20}	0.9712 [5]	d_4^{30}	0.9623 [1]
n_D^{20}	1.4944 [5]	n_D^{30}	1.488 [1]
α_D^{20}	-43.0° [5]	α_D^{30}	-40.1° [1]
semicarbazone m.p.	205-7° [5]	m.p.	206-8° [1]
oxime m.p.	113-114°	m.p.	112° [1]
2,4-Dinitrophenyl-hydrazone m.p.	99-100°	m.p.	101° [1]

Valeranone forms a monobenzylidene derivative (m.p. 101 - 102°) which

[6] J.Plíva, M.Horák, V.Herout and F.Šorm, Catalogue of Spectra In press.

1960

on ozonization affords dicarboxylic acid $C_{15}H_{26}O_4$ (m.p. 236 - 237°). This acid was cyclized, in the presence of barium hydroxide into norvaleranone $C_{14}H_{24}O$ (semicarbazone m.p. 238 - 240°), the infra-red spectrum of which exhibited a band at 1735 cm^{-1}, due to a keto group in a five-membered ring. The ketone formed a liquid monobenzylinede derivative which on ozonization afforded norvaleranic acid $C_{14}H_{24}O_4$ (m.p. 143°). Both on pyrolysis and on treatment with acetic anhydride, the acid afforded a crystalline anhydride $C_{14}H_{22}O_3$ (m.p. 77 - 78°) which on subsequent bromination yielded a crystalline bromo anhydride (m.p. 146 - 148°).

By means of quantitative bromination,[7] the presence in valeranone of two hydrogen atoms in α-position to the keto group was ascertained, i.e. a methylene group and a quaternary carbon atom are adjacent to the carbonyl group. On dehydrogenation, neither valeranol (sulphur, 180°, 4 hr; selenium, 280 - 300°, 1 hr) nor valerene (sulphur, 180°, 1.5 hr; 200 - 250°, 6 hr; iodine 280°, 0.5 hr) afforded any detectable amount of an aromatic derivative (infra-red spectrum) or azulene. Only dehydrogenation of valeranol with

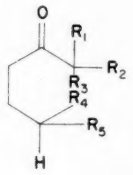
TABLE 2. Comparison of melting points of degradative products

	Valeranone	Jatamansone
Dicarboxylic acid $C_{15}H_{26}O_4$	236-7°	233-234° [1]
Dicarboxylic acid $C_{14}H_{24}O_4$	143°	143° [2]
Anhydride $C_{14}H_{22}O_3$	77-78°	85-86° [2]
Bromo anhydride $C_{14}H_{21}O_3Br$	143°	143° [2]

[7] C.S. Barnes, D.H.R.Barton, A.R.H.Cole, J.S.Fawcett and B.R.Thomas, J.Chem.Soc. 571 (1953).

Pd/C (50%) at relatively high temperature (320 - 340°, 2 hr) led to a mixture of azulenic hydrocarbons.

In view of our present results and in agreement with the statement of Govindachari et al.,[2] valeranone (the identity of which with jatamansone we regard as proved) may be provisionally formulated with a partial structure as follows.



The full experimental data and some new facts about the structure of valeranone will be published in Collection of Czechoslovak Chemical Communications.

Tetrahedron Letters No. 3, pp. 13-16, 1960. Pergamon Press Ltd. Printed in Great Britain.

PHOTODIMERIZATION OF MALEIC AND FUMARIC ACID DERIVATIVES

G. W. Griffin, J. E. Basinski, A. F. Vellturo

Department of Chemistry, Yale University, New Haven, Connecticut

(Received 15 January 1960)

DURING the course of studies directed toward the synthesis of the elusive 1, 2, 3, 4-cyclobutanetetracarboxylic acids[1, 2, 3, 4, 5] and the unknown tetramethylenecyclobutane,[6] we have irradiated several derivatives of maleic and fumaric acid in the solid state with formation of the corresponding cyclobutane derivatives. We wish to report our preliminary results with dimethyl fumarate, fumaronitrile, and maleic anhydride.

The olefins were deposited on the inner surface of a glass tube in a thin layer by evaporation of solvent (ether and/or chloroform). An ultraviolet lamp[7] was then placed in the tube and irradiation was continued for a period of 7-10 days. Cold water passed over the surface of the tube served to dissipate the heat generated in the region of the filaments.

---

1 Y. Shibata, Ber. 43, 2619 (1910).

2 J. Owen and J.L. Simonsen, J. Chem. Soc. 1424 (1932); 1225 (1933).

3 S. K. Ranganathan, J. Ind. Chem. Soc. 13, 419 (1936).

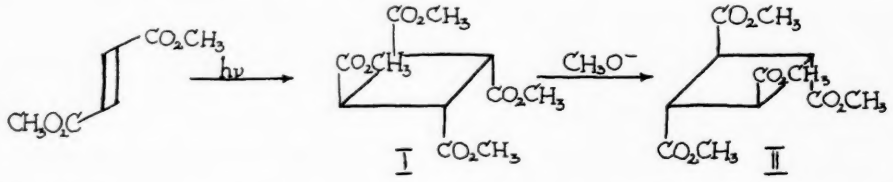
4 E. B. Reid and M. Sack, J. Amer. Chem. Soc. 73, 1985 (1951).

5 E. B. Reid, Chem. and Ind. 846 (1953).

6 J. D. Roberts, A. Streitwieser and C. M. Regan, J. Amer. Chem. Soc. 74, 4579 (1952).

7 Westinghouse 15T8 Germicidal Sterilamp; 95% of the UV radiation in the 253.7 mμ region.

Dimethyl fumarate (10 g), upon irradiation for a period of 10 days, afforded 1, 2, 3, 4-tetracarbomethoxycyclobutane (2 g), m.p. 144-5°.[8] (Found: C, 50.28; H, 5.55; M.W., 263, Rast. $C_{12}H_{16}O_8$ requires: C, 50.00; H, 5.60, M.W., 288). IR, 5.74 (S), 5.80 (M) (C=O),[9] 7.72 (S), 8.33 (M), 9.79 (W), 10.55 (W), 11.85 (W), 12.21 (W). Fortunately, Professor R. Criegee and coworkers have recently synthesized three of the four isomeric 1, 2, 3, 4-cyclobutanetetracarboxylic acids in small quantities by ozonolysis of cinnamic acid dimers of known stereochemistry. Through the kindness of Professor Criegee, mixture melting point determination and comparison of IR spectra show that our ester is identical to his tetramethyl ester of structure I.



Treatment of I with sodium methoxide in methanol effects stereochemical equilibration and leads to an ester, the melting point of which (127°) is identical to that of the all-trans product II, obtained by Professor Criegee.

The NMR data[10] also are in agreement with the assignment of

---

[8] The infrared spectra were all determined in KBr and the results are reported in microns. We wish to thank R. Hager for assistance in obtaining NMR spectra.

[9] Only one peak was present in the carbonyl region when the IR spectrum was determined in chloroform.

[10] G. V. D. Tiers, J. Phys. Chem. 62, 1151 (1958); L. M. Jackman, Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry, p. 50, Pergamon Press, London (1959).

structure I. The spectrum determined in deuterochloroform shows only two types of protons in the expected ratio of 1:3 with the less intense peak at τ = 6.15 and the other at τ = 6.20. The position of the latter peak is consistent with that of the $-OCH_3$ protons of methyl acetate (τ = 6.35). The lack of absorption in the region τ = 3-4 attests to the absence of vinyl protons.

Irradiation of fumaronitrile, under similar conditions (7 days), and recrystallization of the ether-insoluble material from acetonitrile provided a product, m.p. 237-9° (dec), whose elementary analysis, molecular weight and IR spectrum are consistent with those to be expected for 1, 2, 3, 4-tetracyanocyclobutane. (Found: C, 61.31, 61.45; H, 2.71, 2.79; N, 35.91, 35.86. M. W., 152 (ebullioscopic). $C_8H_4N_4$ requires: C, 61.53; H, 2.58; N, 35.88, M.W., 156). IR, 4.43 (S) (C≡N), 3.35 (S), 7.98 (S), 8.25 (S), 8.72 (S), 9.72 (M), 9.54 (W), 9.64 (W), 10.47 (M), 12.22 (S). The stereochemistry is shown to be the same as that of the dimer of dimethyl fumarate (I) by hydrolysis with hydrogen chloride in acetic acid and esterification with diazomethane to yield I.

Maleic anhydride, upon irradiation, yields a high melting product (>200°) which can be isolated by sublimation at 0.005 mm -- first at 93° to remove unreacted maleic anhydride, then at 200°. Its IR spectrum shows the characteristic unconjugated anhydride doublet at 5.40 and 5.62 μ, indicating that it is one of the bis-anhydrides of 1, 2, 3, 4-cyclobutanetetracarboxylic acid (anhydride doublet of cis, cis-3-methylcyclobutane-1, 2-dicarboxylic acid at 5.41 and 5.63 μ).[11] We are

[11] H. N. Cripps, J. K. Williams, V. Tullio and W. H. Sharkey, J. Amer. Chem. Soc. 81, 4904 (1959).

currently in the process of further characterizing this material.

Although we are primarily interested in the use of these products as starting materials for the preparation of novel small ring systems, we plan to study the scope and mechanism of the dimerization by investigating other selected pure, as well as mixed, substrates. Additional data, which should allow us to determine whether or not the stereochemistry of the dimer is inevitably dictated by the crystal structure of the monomer, as is apparently the case with dimethyl fumarate,[12] will be reported at a later date.

The authors are grateful to the Research Corporation for support of this work.

---

[12] I. Ellie Knaggs and K. Lonsdale, J. Chem. Soc. 417 (1942).

Tetrahedron Letters No. 3, pp. 17-24, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

THE STRUCTURE OF NEOLINE

K. Wiesner, H.W. Brewer, D.L. Simmons, D.R. Babin and

F. Bickelhaupt

Organic Chemistry Laboratory, University of New Brunswick

J. Kallos and T. Bogri

Research Laboratory, St. Mary's Hospital, Montreal

(Received 21 December 1959)

IN connection with the structure determination of the Aconitum napellus alkaloids napelline,[1] songorine[1] and aconitine,[2] we have decided to investigate the alkaloid neoline isolated from amorphous aconitine by Freudenberg and Rogers.[3]

The neoline fraction isolated according to these authors was purified by countercurrent distribution, followed by crystallization of neoline, (m.p. 162°). Calc. for $C_{24}H_{39}NO_6$: C, 65.96; H, 9.00; N, 3.21; O, 21.97; $3OCH_3$, 21.30; $C\text{-}CH_3$, 3.43; 3 act. H, 0.69%. Found: C, 65.99; H, 9.03; N, 3.23; O, 21.94; OCH_3, 19.77; $C\text{-}CH_3$, 3.38; act. H, 0.61%. pK_a = 6.7.

We now wish to propose the structure I for this alkaloid. This structure follows from: (a) evidence which shows clearly that the structure of neoline

---

[1] K. Wiesner, Shô Itô and Z. Valenta, Experientia 14, 167 (1958).

[2] K. Wiesner, M. Götz, D.L. Simmons, L.R. Fowler, F.W. Bachelor, R.F.C. Brown and G. Büchi, Tetrahedron Letters No. 2, 15 (1959).

[3] W. Freudenberg and E.F. Rogers, J. Amer. Chem. Soc. 59, 2572 (1937).

and delphinine II[4] are based on the same skeletal system, (b) a successful dehydrogenation of neoline which gave 1-methyl-3-azaphenanthrene (picrate m.p. 208° identified with a synthetic sample) and a phenanthrene $C_{18}H_{18}$ or $C_{19}H_{20}$ (trinitrobenzolate, m.p. 184°). These last results, which are typical of the simple aconite alkaloids,[5] were in turn helpful in the derivation of the delphinine structure.

Neoline yields with acetic anhydride and pyridine a basic oily diacetate. Calc. for $C_{28}H_{43}NO_8$: C, 64.55; H, 8.32; 2 acetyls, 16.51. Found: C, 64.19; H, 8.19; acetyl, 16.13%. With glacial acetic acid and p-toluene sulphonic acid, a crystalline triacetate (m.p. 161°C) was obtained. Calc. for $C_{30}H_{45}NO_9$: C, 64.00; H, 8.06; N, 2.49; 3 acetyls, 22.91. Found: C, 64.10; H, 7.92; N, 2.44; acetyl, 21.36%. I.R.: 1735 cm^{-1} O-acetyl, no hydroxyl peak.

Oxidation of neoline with chromium trioxide gives 1,19-diketoneoline (m.p. 175°). Calc. for $C_{24}H_{35}NO_6$: C, 66.57; H, 8.14; N, 3.23. Found: C, 66.59; H, 8.13; N, 2.97%. pK_a = 4.08. I.R.: 1690, 1745 cm^{-1}. Reduction of diketoneoline with 1 mole of sodium borohydride yields 1-ketoneoline (m.p. 176°). Calc. for $C_{24}H_{37}NO_6$: C, 66.18; H, 8.56. Found: C, 65.76; H, 8.54%. pK_a = 5.03. I.R.: 1695 cm^{-1}. This last compound, on equilibration with sodium methoxide in CH_3-OD followed by exchange of the two alcoholic protons, incorporates two deuterium atoms. (Calc. 5.41 XSS D; Found: 5.70 XSS D).

---

[4] K. Wiesner, F. Bickelhaupt, D.R. Babin and M. Götz, Tetrahedron Letters No. 3, 11 (1959); Tetrahedron In press.

[5] K. Wiesner, J.R. Armstrong, M.F. Bartlett and J.A. Edwards, Chem. & Ind. 132 (1954).

1960

The rotary dispersion curve[6] of 1-ketoneoline is typically affected by the charge of the nitrogen in exactly the same manner as with the delphinine derivatives III,[7] and unlike in the case dihydrodesmethanolaconinone.

1-Ketoneoline shows in chloroform a negative maximum at 323 mμ ($\alpha = -243^{\circ}$) and in glacial acetic acid a positive maximum at 317 mμ ($\alpha = +1450^{\circ}$). Compound III shows maxima at 325 mμ ($\alpha = -300^{\circ}$) and 326 mμ ($\alpha = +1455^{\circ}$) in the same two solvents respectively.

The rotary dispersion curve of the C_{19} keto group in 1,19-diketoneoline is superimposable on the curve of α-axodelphonone[8] (λ_{max} 320 mμ; $\alpha = +1600$). It may be obtained by subtraction of the dispersion curve of 1-ketoneoline from the curve of 1,19-diketoneoline.

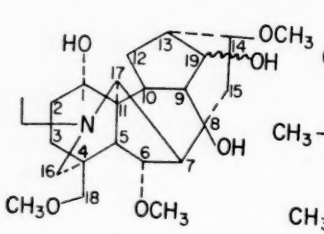
Oxidation of neoline diacetate with potassium permanganate gave a mixture of amides which on mild hydrolysis with alcoholic sodium hydroxide yielded 20% of a secondary base des-(N)-ethylneoline (m.p. 205°). Calc. for $C_{22}H_{35}NO_6$: C, 64.60; H, 8.63. Found: C, 64.84; H, 8.75; $(N)CH_3$, 0.0%. This compound resulted by hydrolysis of the N-acetyl product with participation of the C_1 hydroxyl. Desethylneoline may be converted into neoline by acetylation and reduction of the amorphous acetylation product with lithium aluminium hydride. Methylation of desthylneoline with methyl iodide in methanol in the presence of anhydrous sodium carbonate gave N-methylneoline (m.p. 210°). Calc. for $C_{23}H_{37}NO_6$: C, 65.22; H, 8.81; N, 3.31; $(N)CH_3$, 3.55. Found: C, 65.27; H, 8.80; N, 3.43; $(N)CH_3$, 3.50%.

---

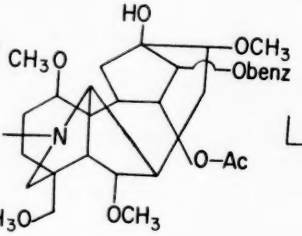
[6] C.Djerassi, R.Riniker and B.Riniker, J.Amer.Chem.Soc. 78, 6362 (1956).

[7] Unpublished derivative prepared by D.R. Babin, Univ. of New Brunswick.

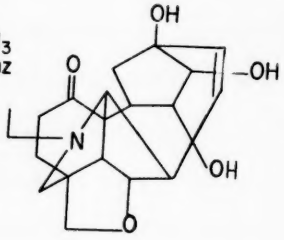
[8] K.Wiesner, F.Bickelhaupt and Z.Valenta, Tetrahedron 4, 418 (1958).



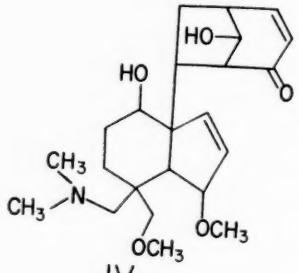
I



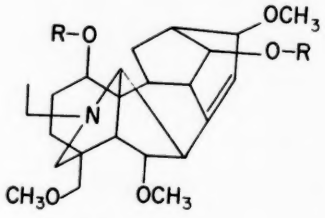
II



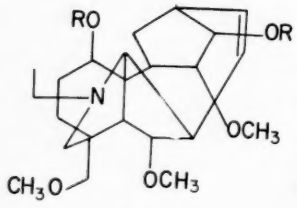
III



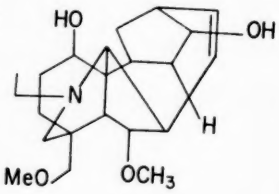
IV



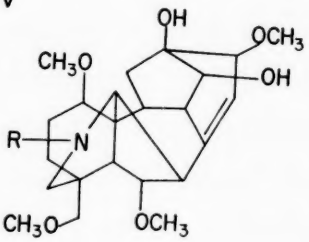
V



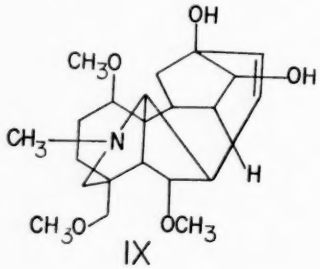
VI



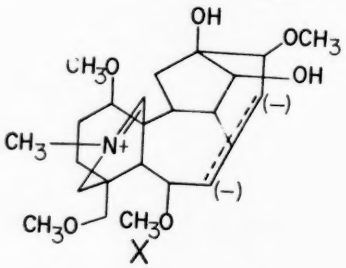
VII



VIII



IX



X

1960

N-methylneoline was quaternized with methyl iodide in nitromethane and the amorphous quaternary salt subjected to an alkaline degradation. By extensive countercurrent distribution a small yield of a crystalline base (m.p. 241°) was isolated from the degradation mixture. Calc. for $C_{23}H_{35}NO_5$: C, 68.12; H, 8.70; N, 3.46; $2OCH_3$, 15.33. Found: C, 67.78; H, 8.51; N, 3.52; OCH_3, 13.84%. I.R.: 1677, 1608 cm^{-1}. U.V.: λ_{max} 232 mμ, log ε = 3.9. This degradation is completely analogous to a similar reaction of delphonine methiodide[4] and the product is formulated as IV.

Neoline triacetate was pyrolysed at 200° and the product pyroneoline diacetate (V, R = Ac) recrystallized from methanol (m.p. 183°). Calc. for $C_{28}H_{41}NO_7$: C, 66.70; H, 8.14; N, 2.78; 2 acetyls, 17.10; $3OCH_3$, 18.46. Found: C, 66.31; H, 8.05; N, 2.62; acetyl, 17.20; OCH_3, 18.78%. I.R.: 1735 cm^{-1} O-acetyl, 1640 cm^{-1} double bond. The N.M.R. spectrum of V (R = Ac) (toluene scale, 40 Mc) shows a doublet at 1032, 1036 c.p.s. with an area 1H due to the C_{15} hydrogen split by the C_{14} hydrogen.

Warming with methanolic perchloric acid converted pyroneoline diacetate into isopyroneoline diacetate VI (R = Ac) characterized as the perchlorate (m.p. 253°). Calc. for $C_{28}H_{41}NO_7 \cdot HClO_4$: C, 55.67; H, 6.96; N, 2.32; Cl, 5.88. Found: C, 55.63; H, 6.75; N, 2.32; Cl, 5.89%. When CD_3OH was used for the above reaction, the resulting VI (R = AC) was shown to contain one deuterated methoxyl. Calc. for $C_{27}H_{38}NO_6(OCD_3) \cdot HClO_4$: 7.15 XSS D. Found: 7.01 XSS D.

Compounds V and VI (R = Ac) may be hydrolysed by alkali to V and VI (R = H) (m.p. 172° and 151° respectively). Calc. for $C_{24}H_{37}NO_5$: C, 68.70; H, 8.83. Found V: C, 68.99; H, 9.05; VI: C, 68.79; H, 8.80%. Both compounds V and VI (R = H) may be hydrogenated to yield nonidentical

dihydroderivatives (m.p. 149° and 180° respectively). Calc. for $C_{24}H_{39}NO_5$: C, 68.40; H, 9.26; Found: dihydro V: C, 68.33; H, 9.47; Dihydro VI: C, 68.24; H, 9.48%.

Acetylation of des(N)ethylneoline with acetic anhydride-p-toluene sulphonic acid gave N-acetylneoline triacetate (m.p. 205°). Calc. for $C_{30}H_{43}NO_{10}$: C, 62.40; H, 7.45. Found: C, 62.36; H, 7.43%. Pyrolysis of this last compound yielded (N(acetyl-pyroneoline diacetate (V, R = Ac; N-acetyl instead of N-ethyl) as a foam which failed to crystallize. Reduction of this last compound with lithium aluminium hydride gave a crystalline compound (m.p. 191°) represented by VII. Calc. for $C_{23}H_{35}NO_4$: C, 70.90; H, 9.00; $2OCH_3$, 15.95. Found: C, 70.80; H, 8.88; OCH_3, 15.85%. The N.M.R. spectrum of VII showed a poorly resolved multiplet with an area 2H centered around 1020 c.p.s. The identical compound VII may be obtained by lithium aluminium hydride reduction of V (R = H or Ac).

An analogous behaviour on reduction is displayed by corresponding delphinine derivatives. Pyrodelphonine VIII ($R = CH_3$) and α-oxopyrodelphonine VIII ($R = C\leqslant^{O}_{H}$) give on lithium aluminium hydride reduction the identical oily product (I.R. and N.M.R. spectrum) IX. Calc. for $C_{23}H_{35}O_5N$: C, 68.20; H, 8.71; $3OCH_3$, 22.99. Found: C, 67.74; H. 8.46; OCH_3, 21.89%. No U.V. spectrum. N.M.R. shows poorly resolved multiplet with an area 2H centered around 1028 c.p.s.

Finally, we wish to report the unexpected spectroscopic properties of compounds V (R = H or Ac). These compounds show an ultraviolet spectrum (V (R = H) λ_{max} 236 mμ, log ε = 3.85; V (R = Ac) λ_{max} 243 mμ, log ε = 3.75), which disappears on acidification and reappears on neutralization. Compound V (N-acetyl instead of N-ethyl) and VI do not show any ultraviolet absorption.

1960

The same spectroscopic anomally occurs in the delphinine series. Pyrodelphonine VIII (R = CH_3) shows a similar spectrum (λ_{max} 245 mμ, log ε = 3.8) which disappears on salt formation and is absent in α-oxopyrodelphonine (VIII, R = $C\lessgtr^{O}_{H}$). The N.M.R. spectra of VIII (R = CH_3) and VIII (R = $C\lessgtr^{O}_{H}$) are completely analogous. Compound VIII (R = CH_3) shows a doublet with an area 1H at 1030-1034 c.p.s. Compound VIII (R = $C\lessgtr^{O}_{H}$) shows the same doublet at 1019-1023 c.p.s. The greater shielding of the C_{15} proton in the basic compound provides us with a possible explanation of the unexpected spectroscopic behaviour.

The double bond in V or VIII is highly strained. This strain might cause that compound VIII should be represented, to a small extent, by the limiting structure X. The model of X shows that there is an overlap of orbitals between the 7-8 or 8-15 double bond and the N-C_{17} double bond. If such a mesomerism is possible it could well give rise to ultraviolet absorption. Alternative explanations involving an equilibrium between VIII and a highly absorbing isomeric species with two conjugated double bonds have been considered, but they seem to be ruled out. In any case, the parallel spectroscopic behaviour of VIII and V is an additional powerful argument for the analogy of the neoline and delphinine structure.

The placement of the C_{18} and C_6 methoxyls in formula I is based on the possibility to obtain certain derivatives of neoline with an internal ether of the type shown in formula III. (The corresponding experiments will be described in a complete publication.)

The configuration of the C_1 hydroxyl has been already commented on. The configuration of the C_{14} mehtoxyl follows from the ease of the allylic rearrangements in compound V. The configuration of the C_6 mehtoxyl must be

exo with respect to the 1,2,3-bicyclooctane system of ring B to account for the easy displacement with ether formation. The absolute configuration of I follows from the coincidence of various rotatory dispersion curves in the neoline and delphinine series (vide supra).

Delphinine has been correlated[9] directly with aconitine, and recently the absolute configuration of aconitine has been established in a brilliant X-ray analysis by Maria Przybylska.[10]

We wish to thank Ciba Pharmaceutical Products Inc., Summit, New Jersey and Hoffman-LaRoche Limited, Montreal for generous financial support of this work. We also wish to thank Mr. N. Kraut for the preparation of neoline triacetate and Mr. R.H. Wightman for the synthesis of 1-methyl-3-azaphenanthrene.

---

[9] K. Wiesner, D.L. Simmons and L.R. Fowler, Tetrahedron Letters No. 18, 1 (1959).

[10] M. Przybylska and L. Marion, Canad. J. Chem. 37, 1843 (1959).

Tetrahedron Letters No. 3, pp. 25-26, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

REACTIONS OF FREE RADICALS AND UNSYMMETRICAL ORGANO-MERCURIC COMPOUNDS

A.N.Nesmeyanov, A.E.Borisov, A.I.Kovredov and E.I.Golubeva

Moscow University

(Received 18 January 1960)

THE benzoyl peroxide-initiated reaction of carbon tetrachloride and symmetrical organo-mercuric compounds has been reported to be as follows:[1]

$$R_2Hg + CCl_4 \longrightarrow RHgCl + RCCl_3$$

In the present study the homolytical exchange reaction was used between fully substituted unsymmetrical organo-mercuric compounds (prepared by the method of K.A.Kocheshkov and R.Kh.Freidlina) and compounds Nos. 1, 2 and 3, following the Grignard method.

Constants for the compounds are presented in the Table. RHgR' compounds react with carbon tetrachloride in the presence of peroxide according to the scheme:

$$(C_6H_5COO)_2 \longrightarrow C_6H_5COO^{\bullet} + C_6H_5^{\bullet} + CO_2$$

$$C_6H_5^{\bullet} + CCl_4 \longrightarrow C_6H_5Cl + CCl_3^{\bullet}$$

$$RHgR' + CCl_3^{\bullet} \longrightarrow R'Hg^{\bullet} + RCCl_3$$

$$R'Hg^{\bullet} + CCl_4 \longrightarrow R'HgCl + CCl_3^{\bullet} \text{ and so on}$$

$$2CCl_3^{\bullet} \longrightarrow CCl_3 - CCl_3 \text{ the chain break}$$

[1] A.E.Borisov, Izv.Akad.Nauk SSSR,Otdel.khim.nauk 524 (1951).

The less electronegative radical always remains attached to mercury in $RHgCl$[2] and the more electronegative one converts to $RCCl_3$. In the case of R and R' radical characteristics close spacing, as in No.7, all four possible combinations $RHgCl$, $R'HgCl$, $RCCl_3$ and $R'CCl_3$, result.

Thus the $\dot{C}Cl_3$ free radical attacks the same mercury attached radical, which undergoes electrophylic attack by hydrogen ions during acid decomposition of $RHgR'$.

No.	Original compounds	Melting points	Isolated compounds and yields (%)
1	$C_6H_5HgC_2H_5$	Oil	C_2H_5HgCl(87%) + $C_6H_5CCl_3$
2	$C_6H_5CH_2HgC_4H_9$	Oil	$C_6H_5CH_2HgCl$(73%) + $C_4H_9CCl_3$(58%)
3	$C_6H_5HgC_4H_9$	Oil	C_4H_9HgCl(76%) + $C_6H_5CCl_3$(72%)
4	$C_6H_5HgC_6H_{11}$	59 - 61°	$C_6H_{11}HgCl$(83%) + $C_6H_5CCl_3$(43%)
5	$C_6H_5HgCH_2C_6H_5$	Oil	$C_6H_5CH_2HgCl$(73%) + $C_6H_5CCl_3$(33%)
6	$C_6H_5HgC_6H_4CH_3$-p	167 - 192°	C_6H_5HgCl(88%) + p-$CH_3C_6H_4CCL_3$(82%)
7	p-$CH_3C_6H_4HgC_6H_4CH_3$-o	159 - 189°	o-$CH_3C_6H_4HgCl$(57%) + o-$CH_3C_6H_4CCl_3$(40%) + p-$CH_3C_6H_4HgCl$(43%) + p-$CH_3C_6H_4CCl_3$(60%)
8	$C_6H_5HgC_{10}H_7$-α	165 - 195°	C_6H_5HgCl(73%) + α-$C_{10}H_7CCl_3$(73%)

[2] M.S.Kharasch and R.Marker, J.Amer.Chem.Soc. 48, 3130 (1926); A.N.Nesmeyanov and K.A.Kocheshkov, Uch.Zap.Mosk.Univ. No.3, 283 (1934).

1960

Tetrahedron Letters No. 4, pp. 1-4, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

SIPHULIN, A CHROMANONE TYPE LICHEN ACID

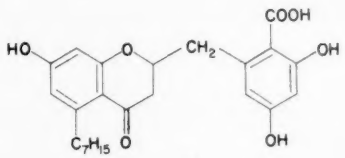
T. Bruun

Institutt for Organisk Kjemi, Norges Tekniske Högskole

Trondheim, Norway

(Received 18 January 1960)

SIPHULA ceratites (Fr.) Th. Fr., an imperfect lichen with a disjunctive distribution in Norway, contains a new type of carboxylic acid for which the name siphulin and the constitution 7-hydroxy-5-n-heptyl-2 [3', 5'-dihydroxy-2-carboxybenzyl] - chroman-4-one (I) are proposed.



I

The acid melted at about 180° with evolution of carbon dioxide (Found: C, 67.7; H, 6.45. $C_{24}H_{28}O_7$ requires C, 67.3; H, 6.6%). Potentiometric titration in ethanol-water (3:2) indicated an equivalent weight of 425 (required M.W.-428). It contained no methoxyl group. The acid was optically inactive, and this was confirmed by optical rotatory dispersion measurements, very kindly carried out by Dr. W. Klyne, London, England. U.V. absorption λ_{max} 2440, 2510, 2635 and 2935, ε 29,500, 30,000, 20,500, 23,500 respectively,

λ_{min} 2410, 2480, 2585 and 2470 Å, ε 29,900, 27,500, 19,500 and 17,500. The infra-red spectrum in KBr gave no information apart from an indication that the substance might be an o-hydroxy carboxylic acid since it contained a very broad, indistinct band at about 1650 - 1660 cm^{-1}.

The acid was characterized by the preparation of a tri-acetate a methyl ester, a dimethoxy methyl ester, a methyl ester tri-acetate, a dimethoxy methyl ester acetate and a trimethoxy methyl ester. Of these the last three substances gave information of the presence of a carbonyl function inert towards the usual carbonyl reagents, as exemplified by the trimethoxy methyl ester: m.p. 77-78° (Found: C, 70.1; H, 7.2; O-Me, 26.5. $C_{28}H_{36}O_7$ requires C, 70.0; H, 7.55; O-Me 25.8%). λ_{max} 2500 and 2860 Å, ε 25,500 and 20,500, respectively, with an inflexion at about 2400 Å, ε 31,000 and λ_{min} at 2490 and 2620 Å, ε 25,000 and 11,500. The infra-red spectrum showed bands at 1730 cm^{-1} (ester) and at 1655 cm^{-1} (conjugated carbonyl group). This trimethoxy methyl ester with N-bromo-succinimide furnished a monobromo compound, m.p. 123-125° (Found: C, 59.7, 59.85; H, 5.9, 6.0; Br, 14.1, 13.9; O-Me, 21.6, 20.4, 20.4; C-Me 3.0, 4.2. $C_{28}H_{35}BrO_7$ requires C, 59.7; H, 6.25; Br, 14.2; O-Me, 22.0; C-Me, 2.65%). λ_{max} 2505 and 2900 Å, ε 24,500 and 20,500, respectively, λ_{min} 2485 and 2610 Å, ε 24,000 and 16,500. The infra-red spectrum showed carbonyl bands at 1730 and 1655 cm^{-1} with a should at about 1670 cm^{-1}.

Alkaline degradation of the acid gave as isolated and identified compounds sphaerophorol (3,5-dihydroxy-n-heptyl-benzene), m.p. 56-57°, 3,5-dihydroxyphenylacetic acid, m.p. 126-127° (anhydrous) and acetic acid (p-bromophenacyl ester, m.p. 85-86°).

Alkaline degradation of the trimethoxy methyl ester afforded, apart

1960

from products with no direct bearing on the constitutional problem, 2-carboxy-3,5-dimethoxyphenylacetic acid, m.p. 174-175°, λ_{max} 2505 and 2835 Å, ε 6100 and 3500, λ_{min} 2370 and 2705 Å, ε 5200 and 2300, a band in the infra-red at 1720 cm^{-1} with a shoulder at 1680 cm^{-1}; and a liquid compound, presumably 2-hydroxy-4-methoxy-6-n-heptylacetophenone, b.p. $110°/10^{-3}$ mm (bath), n_D^{19} 1.5339, bluish-violet colour with ferric chloride (Found: C, 72.8; H, 9.1; O-Me, 11.8; C-Me, 10.5. $C_{16}H_{24}O_3$ requires C, 72.7; H, 9.15; O-Me, 11.7; C-Me, 11.4%), λ_{max} 2700 Å, ε 7000, λ_{min} 2460 Å, ε 3300; a broad band in the infra-red at about 1690 cm^{-1} (liq.).

Oxidation of the trimethoxy methyl ester with selenium dioxide furnished a lactone, m.p. 167-168° (Found: C, 67.1; H, 6.2; O-Me, 19.25. $C_{27}H_{32}O_8$ requires C, 66.9; H, 6.65; O-Me, 19.2%), λ_{max} 2540 and 2960 Å, ε 29,500 and 22,000, λ_{infl} at about 2440 and 2620 Å, ε 29,500 and 19,500, λ_{min} 2500 and 2740 Å, ε 27,000 and 14,000 carbonyl bands in the infra-red at 1772 and 1652 cm^{-1}.

Potassium permanganate oxidation of the lactone afforded 3,5-dimethoxyphthalic acid, identified as the anhydride, m.p. 149-150°, and 2-hydroxy-4-methoxy-6-n-heptylbenzoic acid, m.p. 125-126° (Found: C, 67.4; H, 8.3. $C_{15}H_{22}O_4$ requires C, 67.65; H, 8.35%). λ_{max} at 2175, 2605 and 3020 Å, ε 32,500, 15,000 and 6000, λ_{min} at 2365 and 2800 Å, ε 4400 and 2400, carbonyl band at 1652 cm^{-1} (KBr).

All identifications were secured by comparison of m.p., mixed m.p., u.v. and i.r. spectra with corresponding data for authentic (below) compounds. All ultra-violet absorption spectra were measured in solutions in ethanol on a Perkin-Elmer No. 13 spectrometer, and infra-red spectra on a Perkin-Elmer No. 21 spectrometer.

2-Hydroxy-4-methoxy-6-neheptylbenzoic acid was synthesized from sphaerophoral carboxylic acid, prepared by careful hydrolysis of sphaerophorin by prolonged action of diazomethane followed by saponification. 3,5-dihydroxyphenylacetic acid was synthesized according to Theilacker and Schmid[2] and the p-bromophenacyl ester of acetic acid by the standard method of phenacyl esters. 2-Carboxy-3,5-dimethoxyphenylacetic acid was synthesized from ethyl 3,5-dihydroxy-2-carbethoxyphenylacetate[3] as starting material.

The potentiometric titration was carried out by Mrs. A. R. Alertsen.

Acknowledgements - Thank are due to Professor S. Shibata, Tokyo, Japan, for providing the comparison specimen of sphaerophorol and a sample of sphaerophorin, to Dr. C.A. Wachtmeister, Stockholm, for another sample of sphaerophorin, and to Dr. A.I. Scott, Glasgow, for a sample of 3,5-dimethoxyphthalic acid.

The author also wishes to thank Professor N.A. Sorensen for his interest and assistance in collecting material.

---

[1] K. Faegri, Blyttia 10, 77 (1952).

[2] W. Theilacker and W. Schmid, Liebigs.Ann. 570, 15 (1950).

[3] H. Nogami, J. Pharm. Soc. Japan. 61, 24 (1941); Chem.Zbl. 11, 1276 (1941).

Tetrahedron Letters No. 4 pp. 5-6, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

C-ALKYLIERUNG VON TRIPHENYLPHOSPHIN-CARBOMETHOXY-METHYLEN. EIN NEUER WEG ZUR SYNTHESE VON CARBONSÄUREN

H.J. Bestmann und H. Schulz

Organisch Chemisches Institut der Technischen Hochschule, München

(Received 19 January 1960)

DAS bestandige Triphenylphosphin-carbomethoxymethylen[1] setzt sich mit Methyljodid genau so wie das von Wittig und Rieber untersuchte Triphenylphosphinmethylen[2] um:

$$CH_3J + \underset{\underset{P(C_6H_5)_3}{\|}}{CH}\!\!-\!\!COOCH_3 \longrightarrow [\ \underset{\underset{\oplus\ P(C_6H_5)_3}{|}}{CH_3\text{-}CH_2}\!\!-\!\!COOCH_3\ ]\ J^{\ominus}$$

I II

Die Ausbeute an Triphenyl-α-carbomethoxyäthyl-phosphoniumjodid (II) vom Schmp. 138-140° beträgt beim Arbeiten in siedendem Essigester 75% d.Th.

Dagegen verläuft die Einwirkung von Bromessigsäure-methylester oder Benzylbromid auf das Triphenylphosphin-carbomethoxymethylen(I) unter den gleichen Bedingungen nach folgendem Schema:

$$2\ R\text{-}CH_2\text{-}Br + 2\ (C_6H_5)_3P{=}CH\text{-}COOCH_3 \longrightarrow (C_6H_5)_3P{=}\underset{\underset{CH_2\text{-}R}{|}}{C}\text{-}COOCH_3 +$$

$$[(C_6H_5)_3P^{\oplus}\text{-}CH_2\text{-}COOCH_3]\ Br^{\ominus}$$

V

III R=$COOCH_3$

IV R=C_6H_5

---

[1] O.Isler, H.Gutmann, M.Montavon, R.Ruegg, G.Ryser und P.Zeller, Helv.Chim.Acta 40, 1242 (1957).

[2] G.Wittig und M.Rieber, Liebigs Ann. 562, 177 (1949).

Man erhält das für die Darstellung von I benötigte Triphenyl-carbomethoxymethy-phosphoniumbromid und ein C-Alkyliertes I. Das Triphenylphosphin-(carbomethoxymethyl)carbomethoxy-methylen (III) vom Schmp 158 - 160° entsteht in einer Ausbeute von 80% d.Th., das Triphenylphosphin-(benzyl)carbomethoxymethylen (IV) vom Schmp. 185 - 187° in 75% d.Th. Während der Reaktion fällt das Phosphoniumsalz (V) aus (90% d.Th.) und das Phosphinalkylen bleibt in Lösung.

Bei der alkalischen Hydrolyse zerfällt das Phosphoniumjodid II in Propionsäure und Triphenylphosphinoxyd:

$$[CH_3\text{-}\underset{\oplus P(C_6H_5)_3}{CH} \text{---} COOCH_3]\, J^{\ominus} \xrightarrow{OH^-} CH_3\text{-}CH_2\text{-}COOH + OP(C_6H_5)_3 + CH_3OH$$

Das Phosphinmethylen III ergibt unter den gleichen Bedingungen Bernsteinsäure und die Verbindung V Hydrozimtsäure. Die Ausbeuten an Carbonsäuren liegen zwischen 90 und 100% d.Th.

Damit eröffnet sich ein neuer Weg zur synthese von Carbonsäuren dessen Allgemeingültigkeit zur Zeit an weiteren Beispielen untersucht wird. Weiter wird geprüft, inwieweit die so leicht zugänglichen Phosphinmethylene der Struktur III und IV die Wittig-Reaktion einzugehen vermögen und so gleichzeitig die Darstellung α,β-ungesättigter-α-verzweigter Carbonsäuren ermöglichen.

Tetrahedron Letters No. 4, pp. 7-9, 1960. Pergamon Press Ltd. Printed in Great Britain.

C-ACYLIERUNG VON TRIPHENYLPHOSPHIN-ALKYLENEN. EIN NEUER WEG ZU KETONEN

H.J. Bestmann

Organische Chemisches Institut der Technischen Hochschule, München

(Received 19 January 1960)

TRIPHENYLPHOSPHIN-methylen setzt sich mit Methyljodid nach Untersuchungen von Wittig und Rieber[1] zu Triphenyl-äthylphosphoniumjodid um:

$$CH_2{=}P(C_6H_5)_3 + CH_3J \longrightarrow [CH_3{-}CH_2{-}\overset{\oplus}{P}(C_6H_5)_3]\ J^{\ominus}$$

Weiter fanden Wittig und Schöllkopf,[2] dass Benzoesäureester auf das gleiche Phosphinmethylen folgendermassen einwirkt:

$$C_6H_5{-}\overset{O}{\overset{\|}{C}}{-}OR + \overset{\ominus}{\underset{H}{\overset{H}{C}}}{-}\overset{\oplus}{P}(C_6H_5)_3 \longrightarrow [\,C_6H_5{-}CO{-}CH_2{-}\overset{\oplus}{P}(C_6H_5)_3]\ OR^{\ominus}$$

Dagegen nimmt die Reaktion der Triphenylphosphin-alkylene mit Carbonsäurechloriden einen anderen Verlauf:

$$2\ R{-}CH{=}P(C_6H_5)_3 + R'{-}CO{-}Cl \rightarrow R{-}\underset{\underset{P(C_6H_5)_3}{\|}}{C} \longrightarrow CO{-}R' + [R{-}CH_2{-}\overset{\oplus}{P}(C_6H_5)_3]\ Cl^{\ominus}$$

Man erhält die Triphenylphosphin-acyl-alkylene und Triphenyl-alkyl-phosphoniumchloride, aus denen man erneut das Ylid darstellen kann.

Die Reaktion wird in Benzol vorgenommen. Dabei fällt das Phosphoniumchlorid aus (70 - 90% d.Th.) während das acylierte Phosphinalkylen in Lösung

---

[1] G. Wittig und M. Rieber, Liebigs Ann. 562, 177 (1949).

[2] G. Wittig und U. Schöllkopf, Chem.Ber. 87, 1318 (1954).

bleibt und durch Eindampfen gewonnen werden kann (60 - 80% d.Th.).

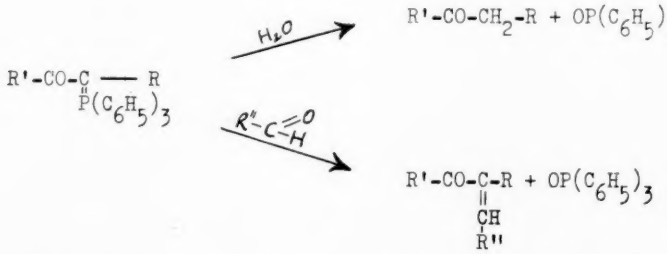
Auf diesem Wege wurden bisher folgende Triphenylphosphin-acyl-alkylene dargestellt:

Triphenylphosphin-acyl-alkylene $R\text{-}C(=P(C_6H_5)_3)\text{-}CO\text{-}R'$

Nr	R	R'	Schmp
I	H	CH_3	200 - 202°
II	H	C_6H_5	178 - 180°
III	CH_3	C_6H_5	170 - 172°
IV	C_6H_5	C_6H_5	192 - 194°
V	C_6H_5	CH_3	166 - 168°

Bei den Verbindungen I-V ist im U.R-Spektrum die Carbonylbande nach 6,5-6,7μ verschoben.[2, 3]

Ramirez und Dershowitz fanden, dass Triphenylphosphin-acyl-methylene bei der Hydrolyse in die entsprechenden Ketone übergehen und mit Aldehyden in einer Wittig-Reaktion α, β-ungesättigte Ketone bilden:[3]



[3] F. Ramirez und S. Dershowitz, J.Org.Chem. 22, 41 (1957).

Während die Triphenylphosphin-acyl-benzylene ($R=C_6H_5$) gegen Hydrolyse weitgehend beständig sind, konnten für die Triphenylphosphin-acyl-alkylene, bei denen R kein aromatischer Kern ist, die Befunde von Ramirez und Dershowitz bestätigt werden. Triphenylphosphin-acetyl-methylen (I) ergab durch Hydrolyse Aceton (83% d.Th.), Triphenylphosphin-benzoyl-methylen (II) Acetophenon (93% d.Th.) und Triphenylphosphin-benzoyl-äthylen Propiophenon (85% d.Th.).

Damit ergibt sich eine neue Methode zur Darstellung von Ketonen aus Carbonsäurechloriden und Alkylhalogeniden, für die zur Zeit weitere Beispiele ausgearbeitet werden. Weiter wird geprüft, in wieweit die Möglichkeit der Anwendung der Wittig-Reaktion auf die so leicht zu gewinnenden Triphenylphosphin-acyl-alkylene zugleich eine allgemeine Synthese α, β-ungesättigter-α-Verzweigter Ketone eröffnet.

Tetrahedron Letters, No. 4, pp. 10-14, 1960. Pergamon Press Ltd. Printed in Great Britain.

PHOTOCHEMICAL REACTIONS OF 20-KETOSTEROIDS

N. C. Yang and Ding-Djung H. Yang

Department of Chemistry, University of Chicago, Chicago 37, Illinois

(Received 20 January 1960)

IN a previous communication from this laboratory,[1] it was shown that ketones having hydrogen atoms at γ-positions under the influence of ultraviolet light give, besides other products, cyclobutanols. Further investigations indicated that isomeric cyclobutanols were formed in these reactions. 2-Octanone (I) under previously reported conditions gave two isomeric 1-methyl-2-propylcyclobutan-1-ols (III): Compound IIIa, b.p. 67 - 68° (9 mm), n_D^{20} 1.4420, phenylurethane, m.p. 78°; Compound IIIb, b.p. 82° (38 mm), n_D^{20} 1.4402, phenylurethane, m.p. 102 - 103°. The structures of these isomers were established by chemical degradation. The cyclobutanols were converted to the corresponding bromides which were dehydrobrominated to mixtures of olefins. The mixtures of olefins showed infrared absorption at 1680 cm^{-1} and 880 cm^{-1} indicating the presence of a methylene cyclobutane.[2] Ozonization of these olefinic mixtures yielded 2-propylcyclobutanone, purified by distillation and gas chromatography, b.p. 73 - 75° (100 mm), ν_{max} 1780 cm^{-1},

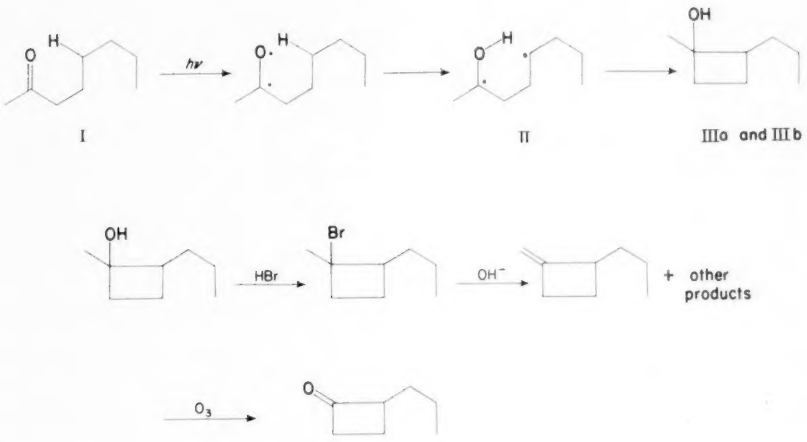
---

[1] N.C. Yang and D.H. Yang, J.Amer.Chem.Soc. 80, 2913 (1958).

[2a] J.D. Roberts and C.W. Sauer, J.Amer.Chem.Soc. 71, 3925 (1949).

[b] R.C. Lord and F.A.Miller, Appl. Spectroscopy 10, 115 (1956).

and 2,4-dinitrophenylhydrazone, m.p. 116°.



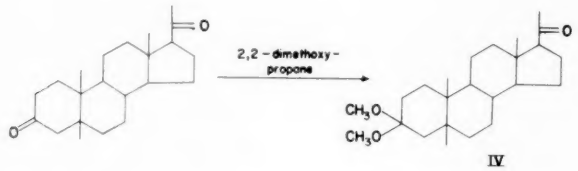
Recently, Jeger and coworkers[3] reported the formation of single isomeric 20-hydroxy-18,20-cyclasteroids from the irradation of 20-ketosteroids. Some of these cyclasteroids are intermediates in the synthesis of 18-oxygenated steroids. To explain the formation of only one isomeric 18,20-cyclasteroid, they postulated a "four-center" reaction mechanism. The results of independent investigation in this laboratory showed that two isomeric 20-hydroxy-18,20-cyclasteroids were actually formed in these reactions.

3,3-Dimethoxypregnan-20-one (IV), prepared by selective ketal interchange between 3,20-pregnanedione and 2,2-dimethoxypropane, was irradiated

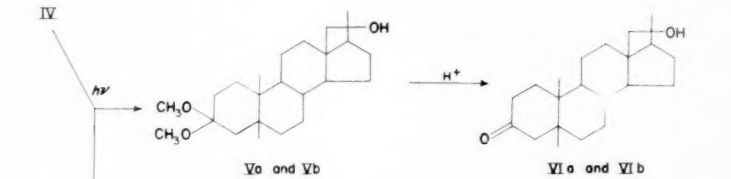
---

[3] O. Jeger et al., Helv. Chim. Acta 42, 2122 (1959).

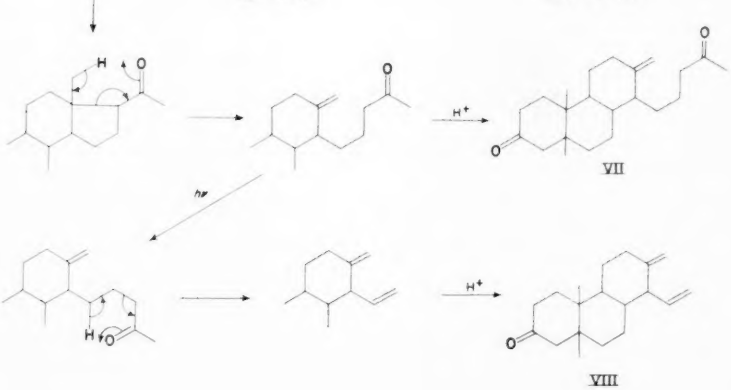
in methanol by means of an immersion apparatus[4] for 16 - 24 hr. Two isomeric 3,3-dimethoxy-18,20-cyclapregnan-20-ols (Va and Vb) were separated from the reaction medium by crystallization and chromatography. Compound Va was isolated in 24 - 35% yield, m.p. 168°, $[\alpha]_D^{25}$ = +29.0° ($CHCl_3$); and Compound Vb was isolated in 8 - 12% yield, m.p. 111 - 112°, $[\alpha]_D^{25}$ = +33.9° ($CHCl_3$). These compounds may be hydrolyzed readily to the corresponding 3-ketones, Compound VIa, m.p. 85 - 86° and Compound VIb, m.p. 175°. In addition to



IV



Va and Vb VIa and VIb



VII

VIII

[4] M.S. Kharasch and H.N. Friedlander, J. Org. Chem. 14, 245 (1949)

these cyclasteroids, two by-products were isolated as their respective 3-ketones (VII and VIII). Compound VII, $C_{21}H_{32}O_2$, m.p. 88 - 89°, is an unsaturated ketone isomeric with pregnanedione with a vinylidene type of unsaturation ν_{max} at 885 and 1640 cm^{-1})[5] which may be derived from a Type II photochemical cleavage[6] of IV involving the 20-ketone function. Compound VIII, $C_{18}H_{26}O$, m.p. 97 - 99°, is a diene with both vinyl and vinylidene types of unsaturation ν_{max} at 885 and 910 cm^{-1})[5] which may be derived from an additional Type II cleavage of the unsaturated ketone VII.

TABLE 1. Nuclear magnetic resonance spectra of 18,20-cyclasteroids

Compound	Methoxyl ($3\text{-}CH_3O$)	$C_{21}\text{-}CH_3$ (CH_3CO)	$C_{21}\text{-}CH_3$	$C_{19}\text{-}CH_3$	$C_{18}\text{-}CH_3$
3,3-Dimethoxypregnan-20-one (IV)	6.97,7.07	8.00		9.15	9.55
3,3-Dimethoxy-18,20-cyclapregnan-20-ol (Va)	6.93,7.03		8.85	9.05	
Vb	6.69,6.87		8.85	8.97	
18,20-Cyclapregnan-20-ol-3-one (VIa)			8.85	9.02	
VIb			8.85	9.02	

[5] L.J. Bellamy, The Infrared Spectra of Complex Molecules (2nd Ed.) p.34. John Wiley, New York (1958).

[6a] C.H. Bamford and R.G.W. Norrish, J.Chem.Soc. 1938, 1544;
[b] W. Davis, Jr. and W.A. Noyes, Jr., J.Amer.Chem.Soc. 69, 2153 (1947).

[7] The NMR spectra were measured with a Varian 40 mc High Resolution NMR spectrometer with superstabilizer. The unit given is according to G.V.D. Tiers, J.Phys.Chem. 62, 1151 (1958). The unit of cps with benzene as external reference may be converted to (τ p.p.m. with Me_4Si as internal reference) by the following formula:

$$\tau = 3.60 + \frac{cps}{40}$$

The structures of 18,20-cyclasteroids V and VI are supported by NMR spectrometry. The NMR spectrum of 3,3-dimethoxypregnan-20-ne shows peaks of methyl groups at 6.97τ, 7.07τ (methoxyl), 8.00τ (C_{21} acetyl methyl), 9.15τ (C_{19} methyl) and 9.55τ (C_{18} methyl). [7,8] The disappearance of methyl peaks in 9.50 region in Compounds Va, VIa, and VIb is indicative of the participation of C_{18} methyl group in these photochemical reactions. The shifting of methyl peak from 8.00 to 8.55 (singlet) shows that the C_{21} methyl is no longer adjacent to a carbonyl group but is attached to a tertiary carbon atom in these compounds.

Isomeric 18,20-cyclasteroids (IX) were also formed from the photolysis of pregnenolene in ethanol, Compound IXa, m.p. 236°, $[\alpha]_D^{25}$ = -27.5° (abs. ethanol) and Compound IXb, m.p. 190°, $[\alpha]_D^{25}$ = -24.2° (abs. ethanol). These isomeric cyclasteroids (IX) may be oxidized with aluminium isopropoxide and cyclohexanone to the corresponding isomeric 18,20-cycla-4-pregnen-20-ol-3-one (X), Compound Xa, m.p. 204 - 205° and Compound Xb, m.p. 163 - 165°. The structures of these compounds are supported by spectroscopic evidence.

The formation of isomeric cyclobutanols in these photochemical reactions are in agreement with the stepwise mechanism postulated earlier. The excited carbonyl function abstracts a hydrogen atom from the γ-position to give a diradical (II) which then cyclizes to give isomeric cyclobutanols. The detail mechanism of this reaction and the relative configuration of these alcohols are currently being investigated.

The authors wish to thank Drs. G.V.D. Tiers, Raphael Pappo and Gerhard Closs for many helpful discussions, Mr. Charles Lee for assistance in the laboratory, and G.D. Searle & Company for financial support of this investigation.

---

[8] J.N. Shoolery and M.T. Rogers, J.Amer.Chem.Soc. 80, 5121 (1958).

Tetrahedron Letters No. 4, pp. 15-17, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

SYNTHESIS OF ROYAL JELLY ACID

G. I. Fray, R. H. Jaeger and Sir Robert Robinson

Research Laboratory, Shell Chemical Company Ltd., Egham, Surrey

(Received 25 January 1960)

ROYAL jelly acid, which was first isolated by Townsend and Lucas[1] and characterized as 10-hydroxydec-2-enoic acid of m.p. 54-56° by Butenandt and Rembold,[2] has recently been found to possess cancer-inhibiting properties under special conditions.[3] When we decided to synthesize this acid its configuration was undetermined and we therefore planed to prepare both stereoisomerides.

We now wish to report briefly the synthsis of trans-10-hydroxy-dec-2-enoic acid of m.p. 64-65°[4] which proved to be identical (mixed melting point and infra-red spectra) with royal jelly acid from natural sources. Specimens were kindly provided by Dr. Rembold of the Max-Planck Institute for Biochemistry, Munich, and by Dr. W. H. Brown of the Ontario Agricultural College, Guelph, Canada, to both of whom we are greatly indebted. Since then data of nuclear magnetic resonance measurements have been published[5]

---

[1] G.F. Townsend and C.C. Lucas, Biochem.J. 34, 1155 (1940).

[2] A. Butenandt and H. Rembold, Z.Physiol.Chem. 308, 284 (1957).

[3] G.F. Townsend, J.F. Morgan and B. Hazlett, Nature, Lond. 183, 1270 (1959).

[4] U.K. Patent Application No. 25692/59 (27.7.1959).

[5] S.A. Barker, A.B. Foster, D.C. Lamb and L.M. Jackman, Nature, Lond. 184, 634 (1959).

which also identify the natural product as the trans-isomer.

We have so far synthesized royal jelly acid by two methods known to be specific for the preparation of trans-α β-unsaturated acids. The first uses the known 10-acetoxy-decanoic acid,[6,7] which we obtained either from undecylenic acid[6] or from castor oil by a modification of a patented procedure.[8] Bromination of the acid chloride, followed by hydrolysis with water, gave crude 10-acetoxy-2-bromodecanoic acid which was successively refluxed with an ethanolic solution of sodium iodide and an aqueous alcoholic solution of sodium hydroxide. Isolation of the acidic material, chromatographic separation on Florex, and repeated crystallizations from ether - light petroleum (b.p. 40 - 60°) of the solid eluted with ether - benzene (10, 20 and finally 50% ether) yielded trans-10-hydroxydec-2-enoic acid as colourless prisms, m.p. 64 - 65°, infra-red max (paraffin paste) at 2.97 (free OH), 5.89 (conjugated C=O), 6.05 (conjugated C=C) and 10.17 μ (trans CH=CH), light absorption max 211 mμ; ε = 12.000 (Found: C, 64.4; H, 9.6 $C_{10}H_{18}O_3$ requires C, 64.5; H, 9.7%).

8-Acetoxyoctanal, which is apparently not recorded in the literature, was the key intermediate for our second synthesis of royal jelly acid. We prepared this aldehyde either from 8-acetoxyoctanoic acid (previously obtained in very poor yield from suberic acid[9] but much more readily available from 6-chlorohexanol[10] by malonic ester synthesis and subsequent

---

6 A. Grün and T. Wirth, Ber. 55, 2206 (1922).

7 P. Chuit, F. Boelsing, J. Hausser and G. Malet, Helv. Chim. Acta. 9, 1074 (1926).

8 U.K. Patent No. 675,434.

9 P. Chuit, Helv. Chim. Acta 12, 463 (1929).

10 W.R. Coleman and W.G. Bywater, J. Amer. Chem. Soc. 66, 1821 (1944).

acetylation) by reduction of the corresponding acid chloride according to Rosenmund, or from 8-acetoxy-1-bromo-octane[11] via 8-acetoxyoctyl toluene-p-sulphonate by oxidation with dimethyl sulphoxide.[12] Thus 8-acetoxyoctanal was obtained as a colourless oil, b.p. 81°/0.3 mm, infra-red max at 3.67 (aldehydic C-H) and 5.75 μ (C=O) (Found: C, 64.3; H, 9.7. $C_{10}H_{18}O_3$ requires C, 64.5; H, 9.7%). Condensation of the aldehyde with malonic acid in pyridine in the presence of a little piperidine at 50° gave trans-10-acetoxydec-2-enoic acid, b.p. 148 - 150°/0.2 mm, infra-red max at 5.78 (C=O), 5.9 (conjugated C=O), 6.07 (conjugated C=C) and 10.2 μ (trans CH=CH) (Found: C, 62.9; H, 8.9. $C_{12}H_{20}O_4$ required C, 63.1; H, 8.8%). Hydrolysis with ethanolic potassium hydroxide yielded trans-10-hydroxydec-2-enoic acid, which after two crystallizations from ether - light petroleum (b.p. 40 - 60°) had m.p. 64 - 65° and was identical with the previously prepared specimen.

---

[11] F.L.M. Pattison, W.C. Howell, A.J. McNamara, J.C. Schneider and J.F. Walker, J. Org. Chem. 21, 739 (1956).

[12] N.Kornblum, W.J.Jones and G.J. Andersen, J. Amer. Chem. Soc. 81, 4113 (1959).

Tetrahedron Letters No. 4, pp. 18-22, Pergamon Press Ltd. Printed in Great Britain.

THE STEREOCHEMISTRY OF NUCLEOPHILIC ADDITION OF THIOPHENOLS TO PROPIOLIC ACID AND ETHYL PROPIOLATE

F. Montanari

Istituto di Chimica Industriale dell'Universitá, Bologna, Italy

(Received 28 December 1959; in revised form 26 January 1960)

β-ARYL-mercapto-acrylic acids, cis (I) and trans (II), were previously prepared by Montanari and Negrini:[1] (I) by base-catalyzed addition of thiophenols to propiolic acid and by nucleophilic substitution of halogen with thiols in cis-β-chloro-acrylic acid, (II) by similar nucleophilic substitution in trans-β-chloro-acrylic acid, by thermal inversion of (I) and by reduction of trans acids (III). The sulphones, sulphoxides, esters and chlorides of acids (I) also undergo thermal inversion in the same sense.

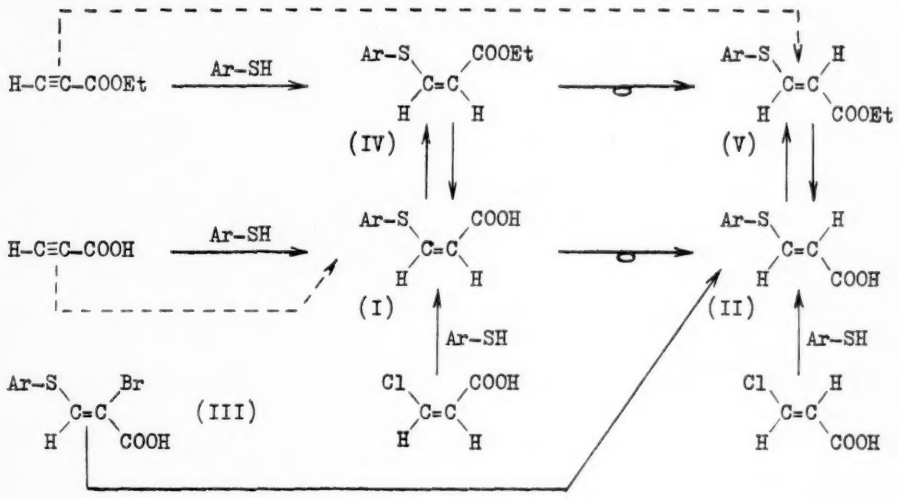
In a recent paper[2] W.E. Truce assigned the opposite configuration to (I) and (II), on the basis of I.R. spectra, dipole moments, and the rate of cyclization of (I) and (II) to thia-chromones. Truce obtained his "trans" acid (I) by addition of p-toluenethiol to propiolic acid,

---

[1] F. Montanari and A. Negrini, Gazz. chim. ital. 87, 1073, 1102 (1957).

[2] W.E. Truce et al., J.Am.Chem.Soc. 81, 4931 (1959); see also: ibid. 79, 5311 (1957).

and his "cis" acid (II) by analogous addition of p-toluenethiol to ethyl propiolate, followed by saponification. (— reactions by Montanari, — reactions by Truce).



Ar = C_6H_5 (I) m.p. 106° (II) m.p. 127-8°

Ar = p-CH_3-C_6H_4- (I) m.p. 143-4° (II) m.p. 137-8°

Thus two opposite mechanisms, of respectively cis and trans addition, would occur in the two cases, with violation of the rule of trans-nucleophilic addition of thiols to triple bond in propiolic acid.

Truce's paper made necessary a complete re-examination of the problem, and we wish to report our principal conclusions.

i) The addition of p-toluenethiol to ethyl propiolate at room temperature for 24 hr, with a catalitic amount of morpholine in ethanol, yields 96%

ester (IV) [m.p. 47-8°, hexane; Found: S, 14.32. $C_{12}H_{14}O_2S$ requires S, 14.42] ; saponification gives acid (I) which may be esterified again to (IV).

Ester (IV) is partially inverted to its isomer (V) by thiolate ion in ethanol at room temperature or by vacuum distillation, i.e. under Truce's conditions. Since ester (V) [b.p. 149.5-150.5° (4 mm), n_D^{20} 1.5752; Found: S, 14.32. $C_{12}H_{14}O_2S$ requires S, 14.42] is identical to the product obtained by Truce [b.p. 134-8° (1.3-1.5 mm), n_D^{20} 1.5748] we may conclude that Truce's conditions are not correct, and the nucleophilic addition of thiols to propiolic acid and ethyl propiolate follows a single steric course.

ii) The I.R. spectrum in Nujol of acid (II) (Ar = C_6H_5) exhibits a strong absorption band at 960 cm^{-1}, absent in (I), which is typical of trans disubstituted ethylenes.[3,4] The same band was recorded by Truce, but it was unaccounted for.

iii) Truce claims to have measured the rate of cyclization to thia-chromones of acids (I) and (II), but under the conditions followed he actual=

---

[3] The Author wishes to express his gratitude to Professor San-ichiro Mizushima of the University of Tokyo, for discussion and interpretation of the infrared spectra. He is also indebted to Prof. A. Foffani of the University of Padua for infrared measurements.

[4] L.J. Bellamy, The Infra-red Spectra of Complex Molecules p. 40. John Wiley, New York (1954); F.A. Miller, in H. Gilman, Organic Chemistry Vol. III, p. 154. John Wiley, New York (1953); W.J. Potts and R.A. Nyquist, Spectrochimica Acta 679 (1959).

ly measured the total rate of chlorination and successive cyclization.

iv) The dipole moments of sulphones related to (I) and (II) may hardly be used as a proof of cis-trans configuration, the true conformation of Ar-SO_2- group in both isomers being unknown.

v) Retention of configuration and no deuteration was found by C.A. Vernon[5] in the reaction products of cis- and trans-β-chloro-ethyl-crotonate and $EtS^{(-)}$, when run in CH_3OD. This is a definitive proof of direct nucleophilic attack on the halogenated carbon, in agreement with the mechanism we proposed for the synthesis of (I) and (II) from cis- and trans-β-chloro-acrylic acids.[1,6]

vi) P-tolyl-mercapto-propiolic acid (VI) Me-C_6H_4-S-C≡C-COOH [m.p. 92-3°, benzene/pet. ether; Found: S, 16.57. $C_{10}H_8O_2S$ requires S, 16.68] is catalitically hydrogenated (Pd-charcoal or Ni-Raney W-5, excess) to give 15% of isomer (I), m.p. 143-4° (all of the remaining product is absorbed by the catalyst and no other compound is isolated). Hydrogenation of (VI) with $NaBH_4$ in diglyme at 0° furnishes quantitatively (II), m.p. 137-8°.[7]

---

[5] Private communication of C.A.Vernon (University College, London) to G.Modena, of this Department; D.E. Jones and C.A. Vernon, Nature 176, 791 (1957).

[6] F. Montanari et al., Boll.sci.Fac.chim.ind.,Bologna 16, 31, 140 (1958); Gazz.chim.ital. 89, 1543 (1959); see also: G.Modena et al., Ricerca sci. 28, 341 (1958); Gazz.chim.ital. 89, 854, 866, 878 (1959).

[7] These conditions are similar to those for trans-hydrogenation of triple bond with $LiAlH_4$ [R.A.Raphael, Acetylenic Compounds in Organic Synthesis Butterworths Scient. Publ., London (1955), p. 29, 202] but differ from cis hydrogenation with $NaBH_4$ and boron trifluoride etherate [H.C. Brown and G.Zweifel, J.Am.Chem.Soc. 81, 1512 (1959)].

vii) In the Diels-Alder reaction with cyclopentadiene, cis acid $C_6H_5-SO_2-CH=CH-COOH$ gives 91% endo adduct (carboxyl), m.p. 198-9°, and 9% exo, m.p. 233-5°, while trans gives 39% endo, m.p. 183°, and 61% exo, m.p. 179-81°,[8] in agreement with the Alder rule.[9]

All these results are consistent with a cis configuration for acids (I) and a trans configuration for acids (II).

---

[8] D. Albera and F. Montanari, research in progress.

[9] K. Alder and G. Stein, Angew. chem. 50, 510 (1937).

1960

Tetrahedron Letters No. 5, pp. 1-5, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

A NEW REACTION OF DIAZOMETHANE WITH α,β-UNSATURATED KETONES

William S. Johnson, M. Neeman and S. P. Birkeland

Department of Chemistry, University of Wisconsin,

Madison, Wisconsin

(Received 29 January 1960)

THERE are no reported instances of a true α,β-unsaturated aldehyde or ketone reacting with an aliphatic diazo compound to effect linear homologation.[1] The reactions instead involve attack of the olefinic linkage to produce pyrazoline derivatives as with benzalacetone,[2] or, if the olefinic bond is unreactive, as in the case of steroid 4-ene-3-ones, no reaction at all is observed.[3]

We have discovered that fluoboric acid, in catalytic amounts, promotes the reaction of diazomethane with α,β-unsaturated ketones to effect homologation, probably by attack at the carbonyl group. Prima facie evidence for the occurrence of this unprecedented reaction was provided when testosterone was submitted to the fluoboric acid-catalyzed diazomethane treatment in

---

[1] C.D. Gutsche in Adams' Org. Reactions VIII, 384 (1954); R. Huisgen, Angew. Chem. 67, 439 (1955).

[2] E. Azzarello, Gazz. Chim. Ital. 36, II, 50 (1906); L.I. Smith and K.L. Howard, J. Amer. Chem. Soc. 65, 165 (1943).

[3] A. Wettstein, Helv. Chim. Acta 27, 1803 (1944); C. Djerassi and C.R. Scholz, J. Org. Chem. 14, 660 (1949); A.L. Nussbaum and F.E. Carlon, J. Amer. Chem. Soc. 79, 3831 (1957).

order to effect methylation of the 17-hydroxyl group.[4] The resulting mixture contained, in addition to the desired methyl ether, a significant proportion of material exhibiting unconjugated carbonyl absorption in the infrared spectrum. Similar results were obtained in the experiment with desoxycorticosterone.[4]

These preliminary findings prompted us to study this reaction with 4-cholestene-3-one. When an excess (4 mole equivalents) of diazomethane in methylene chloride solution was slowly added to a stirred solution of pure[5] cholestenone in methylene chloride containing about 6 mole % of concentrated[4] fluoboric acid, vigorous evolution of nitrogen ensued, and the ultraviolet spectrum of the crude product exhibited relatively weak absorption (ε 6,500) at 241 mμ. Chromatography readily afforded, in 40% yield, a new ketone, m.p. 94-95°, $[\alpha]_D^{25}$ +47.8° (CCl_4), (C, 84.4; H, 11.59), $\lambda_{max}^{CH_2Cl_2}$ 5.84 μ (C=O), 6.1 μ (weak, C=C). The ultraviolet spectrum exhibited only end absorption.

The new ketone gave a yellow color with tetranitromethane, formed a yellow 2,4-dinitrophenylhydrazone, m.p. 189-190° (C, 70.34; H, 8.79), and absorbed 1 mole-equivalent of hydrogen in the presence of palladium catalyst. The nmr spectrum at 60 mc. of a solution of the new ketone in carbon tetrachloride, with benzene as an external standard, gave signals indicating the partial structure $-CH_2COCH_2CH=C$: triplet (J=6) at +80 cps (one vinyl

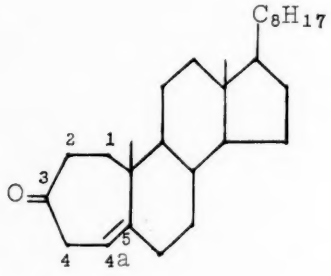
---

[4] M. Neeman, M.C. Caserio, J.D. Roberts and W.S. Johnson, Tetrahedron 6, 36 (1959).

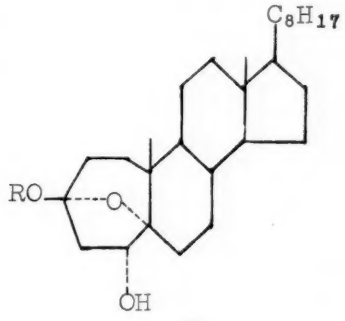
[5] Material was prepared by the procedure of J.F. Eastham and R. Teranishi, Org. Synth. 35, 39 (1955) from cholesterol purified as described by L.F. Fieser, Ibid. 35, 43 (1955). Cholestenone prepared from commerical cholesterol was contaminated with cholestanone and gave difficultly separable mixtures in the diazomethane reaction.

1960

hydrogen, split by two adjacent hydrogens); unresolved multiplet at +208 cps (two hydrogens, allylic to double bond and α to carbonyl); multiplets at +253 and +266 cps (two hydrogens, α to carbonyl group, one showing axial and the other equatorial properties, both split by adjacent hydrogens). The remaining significant features of the nmr spectrum included sharp signals at +324 cps (C_{19} methyl), +333 cps (C_{26} and C_{27} methyls), +339 cps (C_{21} methyl), and +348 cps (C_{18} methyl). Confirmation of the β,γ-unsaturated ketone system was afforded by the appearance of a new band at 6.0 μ in the infrared spectrum of the ketone after it was heated overnight in benzene solution containing a trace of p-toluene sulfonic acid; thus the olefinic bond apparantly was partially isomerized into conjugation with the carbonyl group. It is noteworthy, however, that the equilibrium seems to be in favour of the β,γ-tautomer.



I



II

The foregoing results are consistent with an A homo compound I or the isomeric 4-one-5-ene structure. The latter formulation was excluded by the following experiments. Hydroxylation with osmium tetroxide gave, in high yield, a crystalline product, which was stable to periodic acid and showed no carbonyl stretching absorption in the infrared spectrum. This hydroxylation

product accordingly was formulated as the hemiketal II (R=H). Confirmation of this structure was afforded by its facile conversation, with methanolic hydrogen chloride, into a hydroxy lactol ether (II, R = CH_3), m.p. 177.5-178.5° (C, 77.75; H, 11.17; OCH_3, 6.94). The hydroxyl group of this derivative was shown to be secondary (rather than tertiary as required by the alternative structure mentioned above) by oxidation with chromium trioxide in acetic acid to a keto lactol methyl ether. m.p. 115-116° (C, 78.67; H, 10.83; OCH_3, 7.40). The new ketone, m.p. 94-95°, accordingly may be formulated as A-homo-4a-cholestene-3-one (I).

We have also examined, in a preliminary way, the behaviour of benzalacetone and of benzalacetphenone under these new reaction conditions. Benzalacetone, λ_{max}^{EtOH} 286 mμ (ε 23,500), 220 (12,000), $\lambda_{max}^{CHCl_3}$ 5.98 μ (strong C=O), 6.14, 6.20, was treated for 1 hr with a methylene chloride solution containing 4 mole-equivalents of diazomethane. The significant spectral properties of the crude product were, λ_{max}^{EtOH} 312 mμ (ε 8,100); $\lambda_{max}^{CHCl_3}$ 3.04 μ (N-H), 5.98 (strong, C=O), 6.20, which are indicative of the Δ^2-pyrazoline.[2] When the reaction was repeated as above except that 6 mole % of fluoboric acid was added, the significant spectral properties of the crude product were, λ_{max}^{EtOH} 287 mμ (ε 9,600), 255 (8,700); $\lambda_{max}^{CHCl_3}$ 5.85 μ (strong, C=O), 5.98, 6.14, 6.20 μ. It is clear that in the latter experiment, the carbonyl group was attacked by diazomethane to effect homologation without significant pyrazoline formation. The product clearly contains an unconjugated keto group while the olefinic bond remains largely in conjugation with the benzene nucleus. Similar results were obtained with benzalacetophenone. In the fluoroboric acid-catalyzed experiment no pyrazoline formation was observed, and the extinction coefficient of the absorption maximum at 308 mμ in the

ultraviolet spectrum of the starting material dropped by 25% after the reaction.

Preliminary experiments indicate that comparable results are realized when boron trifluoride is used in place of fluoboric acid.[6]

1960

[6] This work is being supported by grants from the U.S. Public Health Service and the National Science Foundation.

Tetrahedron Letters No. 5, pp. 6-10, 1960. Pergamon Press Ltd. Printed in Great Britain.

SYNTHESIS OF IRIGENIN AND OF TECTORIGENIN, DERIVATIVES OF 5,7-DIHYDROXY-6-METHOXYISOFLAVONE

W. Baker, D. F. Downing, A. J. Floyd, B. Gilbert,

W. D. Ollis and R. C. Russell

University of Bristol

(Received 2 February 1960)

OF the twenty-one known natural isoflavones,[1] three, tectorigenin, irigenin, and caviunin, are derivatives of 5,7-dihydroxy-6-methoxyisoflavone. This particular orientation of substituents makes a direct synthesis difficult, but a method, which we believe to be general, for the synthesis of such isoflavones is now described in the cases of tectorigenin and irigenin. Tectorigenin has previously been synthesised,[2] but it is of interest to note that irigenin, although it

---

[1] W. K. Warburton, Quart. Rev. 8, 67 (1954).
K. Venkataraman, Fortschritte der Chem. Org. Nat. 17, 1 (1959).

[2] S. A. Kagal, S. S. Karmarkar and K. Venkataraman, Proc. Ind. Acad. Sci. 44A, 36 (1956).
L. Farkas, Private communication. Chem. Ber. forthcoming publication.

was the first natural isoflavone to be isolated (in 1893)[3] and its structure was established in 1928,[4] has not hitherto been synthesised.

The main problem in the synthesis of 5,7-dihydroxy-6-methoxyisoflavones (II; R = OH, R' = OMe) from the appropriate deoxybenzoin (I; R = OH, R' = OMe) is that reactions leading to the formation of the heterocyclic ring could give either 5,7-dihydroxy-6-methoxyisoflavones (II; R = OH, R' = OMe) or 5,7-dihydroxy-8-methoxyisoflavones (III; R = OH, R' = OMe). In fact in our first attempt[5] to synthesise tectorigenin (II; R = Y = OH, R' = OMe, X = Z = H), we believed that it had failed because the reaction of the deoxybenzoin (I; R = Y = OH, R' = OMe, X = Z = H) with ethoxalyl chloride had apparently yielded only <u>one</u> product which on hydrolysis and decarboxylation gave an isomer of tectorigenin, Ψ-tectorigenin (III; R = Y = OH, R' = OMe, X = Z = H). However, when the deoxybenzoin (I; R = X = OH, R' = Y = Z = OMe) was treated with ethoxalyl chloride, <u>two</u> isomeric products were formed.[6] This observation led to the following synthesis of irigenin.

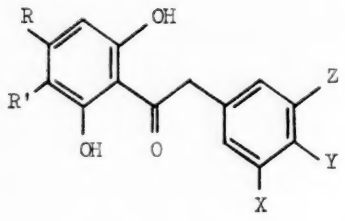
---

[3] G. de Laire and F. Tiemann, <u>Ber.</u> 26, 2010 (1893).

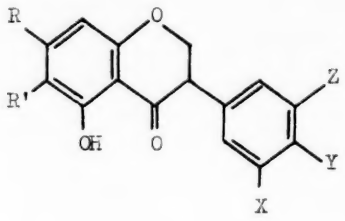
[4] W. Baker, <u>J. Chem. Soc.</u> 1022 (1928).

[5] W. Baker, I. Dunstan, J. B. Harborne, W. D. Ollis and R. Winter, <u>Chem. and Ind.</u> 277 (1953).

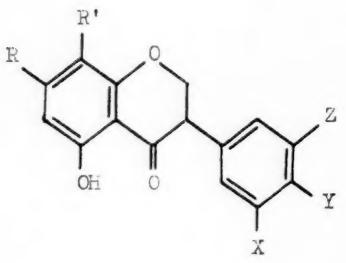
[6] W. Baker and W. D. Ollis, <u>Sci.Proc. Roy. Dublin Soc.</u> 27, No. 6 119 (1956).



(I)



(II)



(III)

Iridonitrile* and iretol (Hoesch reaction) yielded the deoxybenzoin (I; R = X = OH, R' = Y = Z = OMe), m.p. 190-191°, which was identical with the deoxybenzoin obtained from monobenzylirigenin in the following manner. Monobenzylirigenin (II; R = Ph.CH_2O, R' = X = Y = OMe, Z = OH, m.p. 174-175°, diacetate, m.p. 182°) was hydrolysed to the monobenzyl-deoxybenzoin (I; R = Ph.CH_2O, R' = X = Y = OMe, Z = OH, m.p. 133-134°) then debenzylated (Pd-H_2-ethanol). This deoxybenzoin

(I; R = X = OH, R' = Y = Z = OMe) and ethoxalyl chloride-pyridine[7] yielded a mixture of the two possible 2-carbethoxyisoflavones (cf. II and III), since mild alkaline hydrolysis of the product and decarboxylation gave a mixture of irigenin (II; R = X = OH, R' = Y = Z = OMe) and ψ-irigenin (III; R = X = OH, R' = Y = Z = OMe). These were separated by chromatography on thick paper (Whatman No. 1 paper; solvent: benzene, acetic acid, formic acid, water - 8, 2, 1, 1 by volume). The synthetic irigenin, m.p. 190.5-191.5° (from chloroform), m.p. 185-186° (from aqueous ethanol), was identical with the natural product; the isomeric ψ-irigenin m.p. 158.5-159.5°, was characterised as its triacetate, m.p. 146.5-147°.

This successful synthesis of irigenin caused us to re-investigate the reaction carried out earlier[5] which was designed to yield tectorigenin. By analogous methods it was shown that the deoxybenzoin (I; R = Y = OH, R' = OMe, X = Z = H) and ethoxalyl chloride do in fact give two products which have yielded tectorigenin (II; R = Y = OH, R' = OMe, X = Z = H), m.p. 228-230° and ψ-tectorigenin (III; R = Y = OH, R' = OMe, X = Z = H), m.p. 244-246°. This constitutes a new synthesis of natural tectorigenin.

These results disprove our earlier generalisation[5] that ethoxalylation of deoxybenzoins of the type (I) yield 2-carbethoxyisoflavones (cf. III) with a 5,7,8-orientation of substituents. This reaction in fact leads to a mixture of products (cf. II and III) whose composition is certainly

---

[7] W. Baker and W. D. Ollis, Nature 169, 706 (1952).
W. Baker, J. Chadderton, J. B. Harborne and W. D. Ollis, J. Chem. Soc. 1852 (1953).

kinetically controlled. In some other ethoxalylation experiments which we have carried out[8] [e.g. reaction of (I; R = R' = OMe, X = Y = Z = H) or (I; R = R' = Y = OMe, X = Z = H) with ethoxalyl chloride], the products isolated had the 5,6,7-orientation (cf. II), but the yields were lower than is usual in this reaction.

A new isoflavone, caviunin, was recently isolated by Drs. O. R. Gottlieb and M. T. Magalhaes from Dalbergia nigra.[9] It was shown to be 5,7-dihydroxy-6,2',4',5'-tetramethoxyisoflavone and its synthesis by the ethoxalylation method is being studied.

---

[8] I. Dunstan, Dissertation, Bristol (1954).
C. J. Brown, Dissertation, Bristol (1954).

[9] Private communication. We thank Dr. Gottlieb and Dr. Magalhaes for this information.

* Iridonitrile (3-hydroxy-4,5-dimethoxybenzyl cyanide) was synthesised by the following method (B. Gilbert, Dissertation, Bristol 1954). Methyl 3-hydroxy-4,5-dimethoxybenzoate was successively benzylated, reduced ($LiAlH_4$), and treated with thionyl chloride to give 3-benzyloxy-4,5-dimethoxybenzyl chloride; reaction with potassium cyanide and final debenzylation ($Pd - H_2$ - EtOH) gave iridonitrile (an oil giving a benzoate, m.p. 103°).

Tetrahedron Letters No. 5, pp. 11-14, 1960. Pergamon Press Ltd. Printed in Great Britain.

NOVEL SYNTHESIS OF ORGANO- TRI- AND DI-FLUOROSILANES WITH AQUEOUS HYDROFLUORIC ACID

Leonard Spialter

Chemistry Research Branch, Aeronautical Research Laboratory,[1]

Wright-Patterson AF Base, Ohio, U.S.A.

with

Russell S. Towers and Millard M. Kent

Anderson Chemical Company, Weston, Michigan, U.S.A.

(Received 3 February 1960)

WE wish to report the conversion of organo- tri- and di-chlorosilanes to their fluoro-analogs in excellent yields via reaction with aqueous 48% hydrofluoric acid.

It is well-known [2] that halosilanes react readily with water to yield either hydroxysilanes or siloxanes, depending on experimental conditions and molecular structure, with mono-, di-, and tri-halosilanes showing increasing activity in that order. For this reason it has been

---

[1] All work reported was performed at the Aeronautical Research Laboratory.

[2] E. C. Rochow, An Introduction to the Chemistry of the Silicones 2nd. ed. John Wiley and Sons, Inc., New York, N. Y., (1951) p. 9, 24; V. Bazant, V. Chvalovsky and J. Rathousky, Silikony. Statni Nakakladatelstvi Tech. Lit., Prague, Czechoslovakia, (1954) p. 98, 148.

customary to use anhydrous conditions for the preparation of fluorosilanes.[3]

In 1951, Marans, et. al. [4] reported that aqueous hydrofluoric acid may be used with the less readily hydrolyzable organoalkoxysilanes and tri-alkylmonochlorosilanes to yield the corresponding fluoro compounds. We have now found, surprisingly enough, that similar conditions can be applied to di- and tri-chlorosilanes which ordinarily hydrolyze extremely rapidly. In fact, in the presence of excess concentrated aqueous hydrofluoric acid, hydrolysis products of halosilanes have not been isolated by us.

A two-phase mixture of 25.0 g. (0.153 mole) of freshly distilled ethyltrichlorosilane (bp. 96.5 at 745 mm.) and 95 g. of 48% hydrofluoric acid, representing 2.28 moles of HF for a five-fold equivalents ratio, was shaken at 0° in a polyethylene bottle. (No significant reaction was

---

3a H. S. Booth, et al, J. Amer. Chem. Soc. 68, 2650 ff (1946);

b J. Gierut, F. J. Sowa and J. A. Nieuwland, J. Amer. Chem. Soc. 58, 786 (1936);

c F. J. Sowa, U. S. Patents 2,527,233 (1950) and 2,477,704 (1949);

d A. E. Newkirk, J. Amer. Chem. Soc. 68, 2736 (1946);

e E. A. Flood, J. Amer. Chem. Soc. 55, 1735 (1933);

f W. H. Pearlson, T. J. Brice and J. H. Simons, J. Amer. Chem. Soc. 67, 1769 (1945);

g E. Schnell, Monatsh. 88, 1004 (1957).

4 N. S. Marans, L. H. Sommer and F. C. Whitmore, J. Amer. Chem. Soc. 73, 5127 (1951).

observed in the absence of agitation.) The evolved vapors of reaction product, all of which came over in the first hour, were condensed in a dry-ice trap and proved to be essentially pure ethyltrifluorosilane, bp. -5° (Lit. value, bp. -4.4°)[5]; $d_4^{-76.5}$ 1.227; (found: F, 49.1.[6] $C_2H_5F_3Si$ requires F, 49.9). Yields in two parallel runs were 88% and 90%, respectively.

Analogously, 26.4 g. (0.125 mole) of phenyltrichlorosilane (bp. 197 - 199° at 737 mm.) and 78.0 g. of 48% hydrofluoric acid (containing 1.875 moles of HF) were vigorously agitated at 0° for two hours. The phases were separated in a plastic burette and the organic layer washed with water, dried over anhydrous sodium sulfate and the excess hydrogen fluoride absorbed with sodium fluoride. Yield of crude phenyltrifluorosilane was 17.2 g. (85% of theory) boiling at 98 - 104° at 737 mm. (Lit. value, bp. 101 - 102°,[3f] 101.8°)[5]; n_D^{22} 1.4103; (found: F, 35.0.[6] $C_6H_5F_3Si$ requires F, 35.1).

A similar experiment with doubled quantities and, in addition, 200 ml. of n-pentane as diluent gave 83% yield of phenyltrifluorosilane.

The analogous reaction of 63.3 g. (0.25 mole) of diphenyldichlorosilane, in 200 ml. of n-pentane, with 50.0 g. (2.50 moles) of 48% aqueous hydrofluoric acid gave 43.5 g. (86.5%) of diphenyldifluorosilane, bp. 260 - 265° at 737 mm. (Lit. value, bp. 246 - 247°,[3f] 252° estimated)[5]; n_D^{25} 1.5536; (found: F, 17.09.[6] $C_{12}H_{10}F_2Si$ requires F, 17.25).

---

[5] H. J. Emeleus and C. J. Wilkins, J. Chem. Soc. 454 (1944).

[6] Analyzed by volumetric method of reference 4.

Under similar conditions to the above, hexaphenyldisiloxane was not cleaved to give triphenylfluorosilane. This suggests that siloxane formation may not take place prior to establishment of the silicon-fluorine bond and that either direct halogen substitution or, possibly, interaction with the initial hydrolytic products of the chlorosilane may provide the mechanistic route. More work remains to be done to elucidate the scope, limitations and mechanism of this interesting and convenient procedure.

196

Tetrahedron Letters No. 5, pp. 15-19, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

THE ACTION OF DIBORANE AND OF SODIUM BOROHYDRIDE-BORON TRIFLUORIDE-ETHERATE ON ANTHRAQUINONES : A NEW SYNTHESIS OF ALOE-EMODIN AND CITREOROSEIN AND A GENERAL METHOD FOR THE REDUCTION OF ANTHRAQUINONES TO ANTHRACENE DERIVATIVES

D. S. Bapat, B. C. Subba Rao, M. K. Unni
and K. Venkataraman
National Chemical Laboratory, Poona

(Received 3 February 1960)

IN the course of a programme of work on the synthesis of naturally occurring anthraquinone colouring matters[1] the possibility of preparing anthraquinone-2-carbinols, such as aloe-emodin (I) and citreorosein (II), by the reduction of the appropriate derivatives of anthraquinone-2-carboxylic acid was investigated. Reduction of methyl anthraquinone-2-carboxylate in ether by lithium aluminium hydride, followed by air oxidation, gave anthraquinone-2-carbinol in 70% yield,[1] but the method presented difficulties when applied to methyl 4,5-dimethoxyanthraquinone-2-carboxylate for the preparation of (I). Anthraquinone itself, according to two reports, yields anthrahydroquinone (9,10-dihydroxyanthracene)[2] or 9,10-dihydro-9,10-dihydroxyanthracene[3]

---

[1] K. Venkataraman, Festschrift Arthur Stoll p. 360. Birkhauser, Basel (1957).

[2] R.F. Nystrom and W.G. Brown, J. Amer. Chem. Soc. 70, 3738 (1948).

[3] E. Boyland and D. Manson, J. Chem. Soc. 1837 (1951).

by reduction with lithium aluminium hydride under apparently similar conditions.

Chaikin and Brown[4] were unable to isolate boron-free compounds when anthraquinone suspended in dioxane or diethyl carbitol (diethylene glycol diethyl ether) was treated with sodium borohydride. Panson and Weill[5] reported that sodium borohydride in pure diglyme (diethylene glycol dimethyl ether) in an argon atmosphere did not reduce anthraquinone to anthrahydroquinone, but that the reduction took place when diglyme exposed to air for several weeks was used. However, we found that anthraquinone was readily reduced by sodium borohydride in pure diglyme at room temperature to anthrahydroquinone, from which on air oxidation anthraquinone was recovered in nearly quantitative yield; acetylation of the reduction product gave 9,10-diacetoxyanthracene.

Brown and Subba Rao have described the reduction of carboxylic acids to the corresponding primary alcohols by sodium borohydride - aluminium chloride in diglyme or by diborane in any ether medium.[6] Preliminary experiments showed that the former procedure was not suitable for our purpose, and attention was directed to diborane reduction. Diborane, generated by adding a diglyme solution of sodium borohydride to boron trifluoride - etherate in diglyme, was led into a solution of an acetoxyanthraquinone-2-carboxylic acid in diglyme or monoglyme (ethylene glycol

---

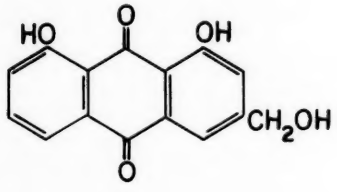
[4] S.W. Chaikin and W.G. Brown, J. Amer. Chem. Soc. 71, 122 (1949).

[5] G.S. Panson and C.E. Weill, J. Org. Chem. 22, 120 (1957).

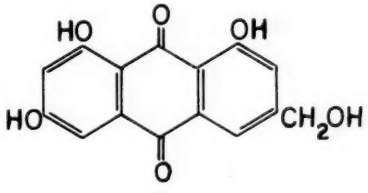
[6] H.C. Brown and B.C. Subba Rao, J. Amer. Chem. Soc. 77, 3164 (1955); 78, 2582 (1956); J. Org. Chem. 22, 1135 (1957).

1960

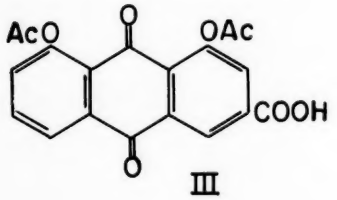
dimethyl ether) at room temperature, until an intense orange to red colour developed; further passage of the gas resulted in the appearance of a bluish green fluorescence and precipitation of a white flocculent boron complex indicating reaction with the quinone group. After 15 minutes ethanol was added and the solvents were removed under reduced pressure. The product, which was the acetoxyanthraquinone-2-carbinol, was dissolved in cold dilute sodium hydroxide solution and acidified. Thus 1-hydroxyanthraquinone-3-carbinol was prepared from 1-acetoxyanthraquinone-3-carboxylic acid, aloe-emodin (I) from rhein diacetate (III), and citreorosein (II) from emodic acid triacetate (IV) in about 60% yield. We are indebted to Professor M. L. Khorana and Professor T. Posternak for samples of natural aloe-emodin and citreorosein. Rhein, emodic acid, chrysophanol and emodin, intermediates for these syntheses, were prepared by the new methods outlined earlier[1] and described in detail in a paper under publication. Aloe-emodin and citreorosein



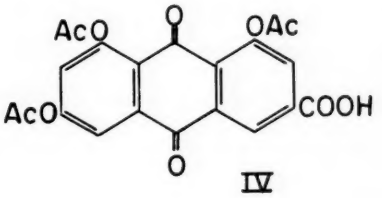
I



II



III



IV

have been synthesised earlier by other workers,[7] but the methods were not free from ambiguity.

An important feature of the action of diborane on anthraquinone-2-carboxylic acids was the preferential reduction of the carboxyl group, the quinone group being attacked only at a later stage. In this connection it seemed desirable to examine the action of a mixture of sodium borohydride and boron trifluoride-etherate, as distinct from diborane, on anthraquinone derivatives, and a new general method for their reduction to anthracene derivatives thus became available. A typical reduction of anthraquinone to anthracene was carried out as follows: To a stirred suspension of anthraquinone (2 g) in diglyme (10 ml) a solution of sodium borohydride in diglyme (10 ml of M solution) was added. The quinone dissolved to a deep red solution with a slight rise in temperature. The flask was externally cooled to 25° and a solution of boron trifluoride-etherate in diglyme (5 ml of 2 M solution) was slowly added during 5 min. The red colour changed to yellow, and a precipitate appeared. The flask was stoppered and magnetically stirred for 2 hr at 25 - 30°. The reaction proceeded with a colour change from yellow to pale cream and the development of fluorescence in ultra-violet light. At the end of the reaction the mixture was acidified to destroy the excess of hydride and the solvent was removed under reduced pressure. The residue was extracted with hexane, and the solution run through a short column of alumina. The colourless fluorescent percolate yielded anthracene (1.25 g). A modification of the procedure was to add a solution of boron trifluoride-etherate and sodium borohydride in diglyme to a solution or suspension of the quinone in diglyme. The time of reaction had to be increased in some

[7] For references see R.H. Thomson, Naturally Occurring Quinones. Butterworths, London (1957).

1960

cases to 3 or 4 hr and the temperature to 50 - 60°. The following reductions have been carried out in yields of 60 - 70%: 1-chloroanthraquinone ⟶ 1-chloroanthracene; 2-chloroanthraquinone → 2-chloroanthracene; 2-aminoanthraquinone → 2-aminoanthracene; 2-hydroxyanthraquinone → 2-hydroxyanthracene; 2-methoxyanthraquinone → 2-methoxyanthracene; anthraquinone-2-carboxylic acid → anthracene-2-carbinol; 3,4,9,10-dibenzopyrene-5,8-quinone → 3,4,9,10-dibenzopyrene;[8] 2-methyl-1,4-naphthoquinone → 2-methylnaphthalene.

2-Methyl-1-nitroanthraquinone gave 2-methyl-1-nitroanthracene in a yield of about 30%, but byeproducts were formed which are under examination. The sodium borohydride-boron trifluoride etherate reagent also provides a convenient method for the reduction of the carbonyl group in chromones and chromanones to the methylene group.

---

[8] Cf. B. D. Tilak, M. K. Unni and K. Venkataraman, Tetrahedron 3, 62 (1958).

Tetrahedron Letters No. 5, pp. 20-23, 1960. Pergamon Press Ltd. Printed in Great Britain.

ON THE STEREOSELECTIVE SYNTHESIS OF ESTRONE

D. K. Banerjee and K. M. Sivanandaiah

Department of Organic Chemistry, Indian Institute of Science,

Bangalore

(Received 27 November 1959; in revised form 28 January 1960)

WITH a view to building the estrone nucleus Banerjee et al.[1] prepared the model compound (Ia), which was also later reported by Turner.[2a] The methoxy derivative (Ib), obtained by Turner[2b] and by Johnson et al.,[3a,b] was stereoselectively converted into estrone by the latter workers. The route is the most practicable one for estrone except for the disadvantage that the key intermediate (Ib) is obtained as one of the two isomers in 43% yield.[3b] A more stereoselective preparation of the bicycle compound (Ib) by an ingenious method was reported by Bhattacharyya et al.[4] Recently a new stereoselective synthesis of estrone has been reported by Cole, Johnson,

---

[1] J. Dutta and D.K. Banerjee, Sci. & Cult. 12, 408 (1947).

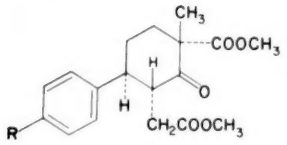
[2a] D.L. Turner, J. Amer. Chem. Soc. 73, 3017 (1951); [b] Ibid. 73, 1284 (1951).

[3a] W.S. Johnson and R.G. Christiansen, J. Amer. Chem. Soc. 73, 551 (1951); [b] W.S. Johnson, R.G. Christiansen and R.E. Ireland, Ibid. 79, 1995 (1957).

[4] P. Sen Gupta and B.K. Bhattacharyya, J. Indian Chem. Soc. 31, 337 (1954); cf. also J.O. Jilek, V. Simak and M. Protiva, Chem. Listy 47, 874 (1953); Chem. Abstr. 49, 197 (1955).

1960

Robins and Walker.[5]



I a, R=H
b, R=OCH_3

In view of the reference[6] to an unpublished work of Johnson, Ireland and Tarney on the development of an improved method for the preparation of Ib, we place on record the experiments carried out by us for a stereospecific synthesis of the same keto diester. It appeared to us that reduction of the double bond in conjugation with the benzene nucleus present in the intermediates [2b,3b] at the earlier stages of preparation of Ib led to a mixture of isomers. We, therefore, at first studied the stereospecific reduction of the unsaturated keto acids (Va and Vb), which were prepared by the following new method.

β-Dimethylamino-p-methoxypropiophenone hydrochloride (II) was condensed with the β-ketoadipic esters (IIIa and II_o) in presence of sodium and ethozide and dimethyl sulphate.[7] The resulting products (IVa and IVb) on

---

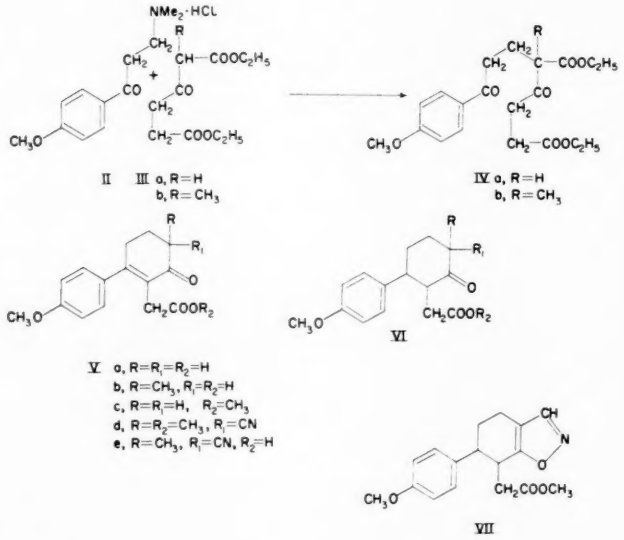
[5] J.E. Cole, Jr., W.S. Johnson, P.A. Robins and J. Walker, Proc. Chem. Soc. 114 (1958).

[6] L.F. Fieser and M. Fieser, Steroids p.500. Reinhold Publishing Corporation (1959).

[7] W.S. Johnson, J.S. Belew, L.J. Chinn and R.H. Hunt, J. Amer. Chem. Soc. 75, 4995 (1953).

treatment with methanolic sodium methoxide furnished 1-p-anisyl-4-methoxycarbonyl-3-ketocyclohexene-2-acetic acid, m.p. 164°;[2b,3b] and 1-p-anisyl-4-methyl-4-methoxycarbonyl-3-ketocyclohexene-2-acetic acid, m.p. 127°.[3b] Hydrolysis of the aforementioned ester acids, as well as refluxing of IVa and IVb with 10% aqueous potassium hydroxide afforded the unsaturated keto acids (Va, m.p. 136°;[3b] and Vb, m.p. 146°), which on reduction with lithium and liquid ammonia[8] gave stereospecifically the saturated acids (VIa, m.p. 111°; yield 82%; and VIb, m.p. 136°, undepressed on admixture with an authentic sample;[4] yield 81%).

A stereospecific synthesis of the keto diester (Ib) starting from the saturated keto ester (VIc), m.p. 68°, was achieved via the isoxazole (VII),



[8] D.K. Banerjee, S. Chatterjee and S.P. Bhattacharya, J. Amer. Chem. Soc. 77, 408 (1955).

b.p. 145-150°/0.006 mm; yield 63%, and the methylated cyano keto ester (VId), m.p. 122°; yield 75%. Treatment of VId with methanolic hydrogen chloride gave Ib, m.p. 93°, undepressed on admixture with an authentic sample; yield 72%. Partial saponification of VId yielded the acid (VIe), m.p. 145°.

The unsaturated cyano keto acid (Ve), m.p. 126°, prepared from the unsaturated keto ester (Vc) via the corresponding isoxazole, m.p. 77-79°, on reduction with lithium and ammonia followed by treatment with methanolic hydrogen chloride also stereoselectively furnished the keto diester (Ib), but in lower yield.

Acknowledgements - We are indebted to Professor W.S. Johnson and Professor B.K. Bhattacharyya for supplying authentic specimens of Ib and VIb respectively. One of us (K.M.S.) is grateful to the University of Mysore for the award of a predoctorial scholarship.

Tetrahedron Letters No. 5, pp. 24-27, 1960. Pergamon Press Ltd. Printed in Great Britain.

MONASCORUBRIN

B.C. Fielding, E.J. Haws, J.S.E. Holker,

A.D.G. Powell, A. Robertson, D.N. Stanway

and W.B. Whalley

Department of Organic Chemistry,

The University, Liverpool,

(Received 22 January 1960; in revised form 5 February 1960)

WE recently reported[1] that rubropunctatin, a pigment from Monascus rubropunctatus Sâto has structure (I). Parallel with this investigation we have examined 'monascorubrin'[2] first isolated by Nishikawa[3] from Monascus purpureus Wentii. Although our work on this substance is incomplete, a recent publication[4] in which structure (IV) is suggested for monascorubrin makes it desirable to record some of our observations, particularly as these

---

[1] E.J. Haws, J.S.E. Holker, A. Kelly, A.D.G. Powell and A. Robertson, J. Chem. Soc. 3598 (1959).

[2] As will become apparent in the sequel 'monascorubrin' is a mixture of rubropunctatin and a second component, present in major amount and for which we now reserve the name monascorubrin. In this communication trivial names enclosed in quotation marks refer to mixtures.

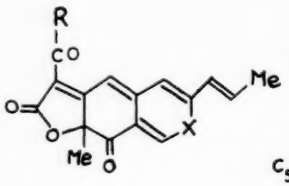
[3] H. Nishikawa, J. Agric. Chem. Soc. Japan 8, 1007 (1932).

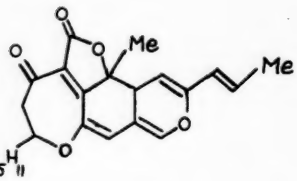
[4] K. Nakanishi, M. Ohashi, S. Kumasaki and S. Yamamura, J. Amer. Chem. Soc. 81, 6339 (1959).

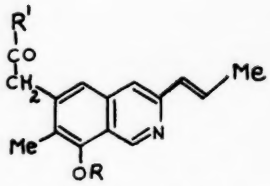
1960

allow us to exclude structure (IV) and to propose a more suitable alternative.

For a long time we were unable to differentiate between rubropunctatin and 'monascorubrin' since both compounds underwent parallel reactions and corresponding products derived from the two natural products exhibited closely similar properties. Thus, 'monascorubrin', m.p. 134-136° (decomp.) $[\alpha]_D$ - 3390° (c 1.03 in $CHCl_3$) λ_{max} (cyclohexane) 236 (sh.), 246, 278 and 410 mμ (log ε 4.17, 4.20, 4.07 and 4.40) ν_{max} 1757(s), 1727(s), 1658(s), 1631(s) and 1570(s) cm.$^{-1}$ (Found: C, 71.7; H, 6.9; (C)-Me, 11.3%) on treatment with dilute ammonium hydroxide gave 'monascorubramine', m.p. 198° (decomp.) λ_{max} (in 95% ethanol) 255, 306, 375(sh.), 430 and 560 mμ (log ε 4.11, 4.35, 4.00, 3.94 and 3.91) ν_{max} 3188(m), 1734(s), 1712(s), 1645(w), 1620(m), 1605(s), 1568(s) and 1530(s) cm^{-1} (Found: C, 71.8; H, 6.9; N, 3.7%). Reduction of 'monascorubramine' with zinc and acetic acid gave one molecular equivalent of carbon dioxide and 'apomonascorubramine' m.p. 190° λ_{max} 257, 305 and 358 mμ (log ε 4.72, 3.84 and 3.67) ν_{max} 3125 (m sh.), 1712(s), 1656(w), 1634(s), 1592(w) and 1570(s) cm^{-1} (Found: C, 77.9; H, 8.4; N, 4.3%) which was characterised as the 'methyl ether', m.p. 65° (Found C, 77.3; H, 8.4; N. 4.5; OMe, 9.0%) and as an 'O-acetate', m.p. 82° (Found: C, 75.0; H, 7.9; N, 4.0; Ac, 10.4%). These compounds have closely similar properties to rubropunctatin (I), rubropunctatamine (II), aporubropunctatamine (V), O-methyl-aporubropunctatamine (VI) and O-acetylaporubropunctatamine (VII) respectively. Analogues of all derivatives of rubropunctatin so far reported[1] have been prepared from 'monascorubrin'. In each case a close parallel exists. The only consistent difference between the two series is that 'monascorubrin' derivatives have a slightly higher carbon and hydrogen content that the corresponding rubropunctatin derivatives.







I R=C_5H_{11} X=O

II R=C_5H_{11} X=NH

III R=C_7H_{15} X=O

IV

V R=H R'=C_5H_{11}

VI R=Me R'=C_5H_{11}

VII R=Ac R'=C_5H_{11}

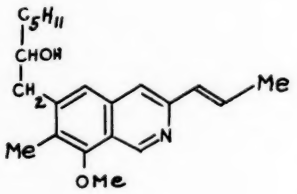
VIII R=Me R'=C_7H_{15}

The situation has now been resolved by comparative mass spectrometric examination of 'O-methylapomonascorubramine' and the corresponding rubropunctatin derivative (VI) when it was found that whereas the latter compound was essentially one component of M.W. 325 in agreement with formula (VI), the former substance was a mixture of two major components of M.W.'s 325 and 353 present in an approximate ratio of 1:4. Gas liquid chromatography showed that the component M.W. 325 had the same retention time as (VI). Thus the component M.W. 353 probably differs from compound (VI) only by two additional methylene groups. The position of these methylene groups has been established by oxidation of 'dihydroapomonascorubramine' (in which the double bond of the propenyl group has been saturated) with potassium permanganate and isolation of the aliphatic carboxylic acids by steam distillation. Separation of these acids as their ammonium salts on paper gave two spots having R_f values of hexanoic and octanoic acids respectively. Thus 'O-methylapomonascorubramine' appears to be a mixture of compounds (VI) and (VIII) and hence 'monascorubrin' as isolated by us is a mixture of rubropunctatin (I) and (III) now called monascorubrin. Although

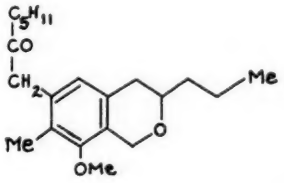
the Japanese workers[4] do not state that their monascorubrin is a mixture this seems likely since the melting point of their substance is identical with that of ours.

The formula (III) for monascorubrin, unlike formula (IV) is in complete agreement with the biogenesis of rubropunctatin recently suggested.[1]

It should be noted that structure (I) for rubropunctatin is derived from the structure (V) for aporubropunctatamine. The evidence previously presented[1] for this structure did not completely exclude other possibilities, but we have now shown that there is an unsubstituted position para to the phenolic hydroxyl group and hence, that aporubropunctatamine is correctly represented by structure (V). Thus, the alcohol (IX) derived from O-methyl-aporubropunctatamine was treated with methyl iodide to give the methiodide, m.p. 118-120° (decomp.) (Found: C, 55.8; H, 7.1; N, 2.9. $C_{22}H_{32}O_2NI$ requires C, 56.3; H, 6.9; N, 3.0%). Oxidation of this with alkaline potassium permanganate gave anisole-2:3:5:6-tetracarboxylic acid, characterised as the tetramethyl ester. The same acid has also been isolated by similar oxidation of O-methylhexahydroaporubropunctatin (X).



IX



X

Acknowledgements - The authors express their gratitude to Dr. J.B. Matthews of the Thornton Research Centre, Shell Refining Co.Ltd. for arranging the mass spectral determination and Mr. A. Quayle for performing these measurements and interpreting the results.

Tetrahedron Letters No. 6, pp. 1-9, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

THE STRUCTURE OF ECHITAMINE[1]

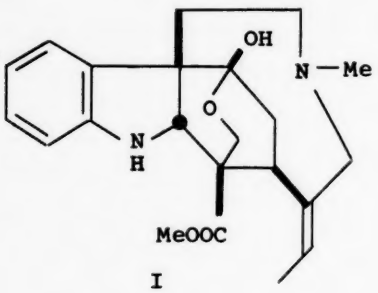
Harold Conroy, Raymond Bernasconi, Peter R. Brook, Raphael Ikan,

Roberta Kurtz and Keith W. Robinson

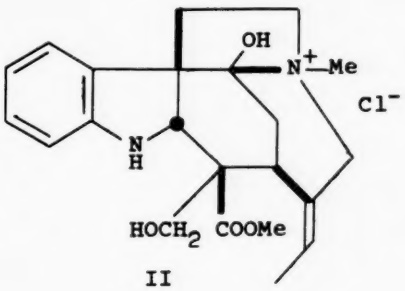
Department of Chemistry, Yale University, New Haven, Connecticut

(Received 1 February 1960)

RECENT literature[2-5] indicates awakened interest in the constitution of the alkaloid echitamine, isolated nearly a century ago from Alstonia scholaris. We now point out that data accumulated elsewhere and in this Laboratory



I



II

---

[1] Contribution 1599 from the Sterling Chemistry Laboratory at Yale University.

[2] T.R. Govindachari and S. Rajappa, Proc. Chem. Soc. 134 (1959).

[3] A.J. Birch, H.F. Hodson and G.F. Smith, Proc. Chem. Soc. 224 (1959).

[4] T.R. Govindachari and S. Rajappa, Chem. & Ind. 1154 (1959); Ibid. 1549 (1959).

[5] S. Ghosal and S.G. Majumder, Chem. & Ind. 19 (1960).

show singular compatibility with the expression (I), originally deduced by one of us from the tenets of the theory of alkaloid biogenesis. Indeed this structure very closely resembles those of certain intermediates long considered prominent in the scheme of natural elaboration of complex indole alkaloids, particularly of the strychnine-vomicine group.

Echitamine chloride (or hydrochloride), $C_{22}H_{29}O_4N_2Cl$,[6-8] for which we favor the expression (II), shows no infrared $\overset{+}{N}$-H peak and no absorption near 1680 cm^{-1} to be ascribed to $>C=\overset{+}{N}<$; the ester carbonyl appears at 1740 cm^{-1}. An aqueous solution of the salt is neutral, and titration shows an apparent pK_a near 11. The action of aqueous sodium hydroxide gives echitamine base, $C_{22}H_{28}O_4N_2$, previously obtained amorphous (ref. 7) ("base A")[3], but now readily crystallized as the benzene solvate, m.p. 139 - 140°

---

[6] O. Hesse, Liebigs Ann. 176, 326 (1875); Ibid. 203, 144 (1880).

[7] J.A. Goodson and T.A. Henry, J. Chem. Soc. 127, 1640 (1925); J.A. Goodson, Ibid. 2626 (1932).

[8] We reject the conslusion of Govindachari and Rajappa (ref. 4) that the empirical formula of echitamine chloride, long established as $C_{22}H_{29}O_4N_2Cl$, should be revised to $C_{22}H_{27}O_3N_2Cl + H_2O$. The Indian workers base their O_3 formulation on the composition of the derivative they call dihydroechitamine, which does contain only three oxygen atoms. But neither echitamine chloride nor echitamine base can be obtained "anhydrous" in this sense. We would be idle not to ask if the salt should crystallize from absolute methanol with a water molecule and a molecule of methanol of crystallization (ref. 7), or if the base should be obtained as a monohydrate, containing as well a molecule of benzene, from its solution in dry benzene. Certain very convincing experiments prove that the fourth oxygen is really part of the molecule; for example, Goodson and Henry (ref. 7) obtained from the chloride a diacetyl derivative ($C_{26}H_{33}O_6N_2Cl$), whose preparation and composition we have confirmed, which shows no amide or $\equiv\overset{+}{N}$-H absorption in the infrared. This derivative is clearly an O,O-diacetate and its formation requires that the two oxygen atoms aside from those in the carbomethoxyl group be present as hydroxyl group in echitamine chloride. We remain with the sole alternative

(Cont'd)

(transition at 98 - 101°) (Found, for an air-dried sample: C, 72.43; H, 7.41; N, 6.22. $C_{22}H_{28}O_4N_2 \cdot C_6H_6$ requires: C, 72.70; H, 7.41; N, 6.06.). The 60 mc high resolution NMR spectrum of echitamine in deuteriochloroform fully supports previous conclusions with regard to the more obvious functional groupings; thus the O-methyl and N-methyl are clearly visible as intense singlets at τ = 6.30 and 7.76, respectively. The position of this N-methyl peak is quite normal for methyl bonded to tertiary nitrogen and indicates conclusively that echitamine is not a quaternary ammonium hydroxide. The allylic C-methyl appears as a doublet[9] (J = 6.4 cps) centered at τ = 8.39, consistent with its proximity to a singlet olefinic proton in the ethylidene group[10]; the olefinic proton appears as a 1:3:3:1 symmetrical quartet (J = 6.4 cps) centered at 4.56. The one-proton singlet near 5.1 is solely, but markedly, concentration dependent and is ascribed to a single hydroxyl in echitamine base.

Normal behavior as a tertiary base was further indicated in the formation of echitamine α-methiodide, with two N-methyl groups, just one of several crystalline salts isolated from reactions with methyl iodide. (Crystals from absolute ethanol, m.p. 226 - 229°, dec. Found: C, 52.22; H, 5.99; N, 5.30; OMe, 5.94; NMe, 9.05. $C_{23}H_{31}O_4N_2I$ requires: C, 52.46, H, 5.94; N, 5.32; OMe, 5.89; two NMe, 11.03.). The reconversion of echitamine to

---

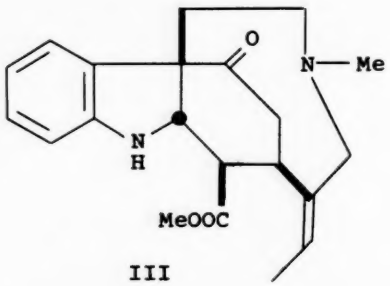
to the proposition of ref. 4, namely that the proximate product of hydrogenation is so remarkably constituted that it can lose one of its oxygen atoms spontaneously.

9 Under highest resolution, each member of the doublet is found to be further split, with about 0.5 cps separation, through longer range coupling with one or more of the other allylic protons.

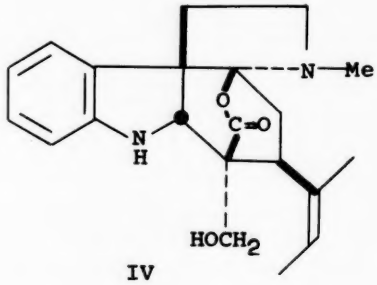
10 The presence of the ethylidene group was shown previously (ref. 3) as was the presence of the sec-butenyl group in "base B" of ref. 3; chromic acid oxidation of the reduction product, "base C", gave α-methylbutyric acid.

echitamine chloride, accomplished readily enough at 100°, is sufficiently slow at 25° so that titration of the base gives a different Pk_a (7.8; 60% aqueous ethanol); this hysteresis in the interconversion of the quaternary chloride (with two hydroxyl groups)[8] into the tertiary base (with only one hydroxyl) is well accommodated by the equilibrium I $\rightleftharpoons$ II.

The reaction of echitamine chloride with potassium t-butoxide in absolute t-butyl alcohol yields, among other products, a substance we call alloechitamine, m.p. 191° from methanol (Found: C, 71.16; H, 7.65; N, 7.85; M.W. (Rast) 327. $C_{21}H_{26}O_3N_2$ requires: C, 71.16; H, 7.39; N, 7.90; M.W. 354), whose composition indicates the loss of the elements of hydrogen chloride and



III

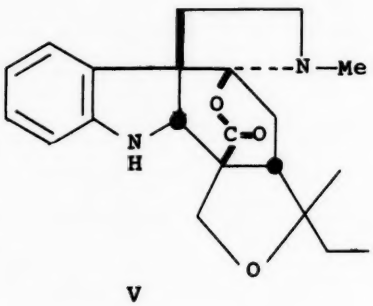


IV

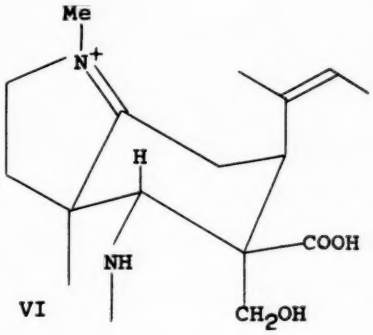
of formaldehyde. The easy removal of one carbon, by dealdolization, constitutes significant evidence for the presence of the system $HOCH_2$-C-COOMe in II. The ketonic carbonyl, masked in other echitamine derivatives, appears in the infrared spectrum of alloechitamine as a strong peak at 1689 cm^{-1}, in addition to that at 1736 cm^{-1}, associated with the ester; there is no hydroxyl absorption. The ultraviolet spectrum shows little change from that of echitamine base, and the NMR spectrum shows that the O-methyl, N-methyl and ehtylidene groups are still present. We consider alloechitamine to be III. The 1689 cm^{-1} carbonyl peak vanishes in the spectrum of alloechitamine

methiodide, containing the grouping $[MeO-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{N}}-Me]^+$; we recall similar evidence of transannular interaction in the formation of the methoperchlorate of N-methylpseudostrychnine.[11]

Returning to formula (II), we see that no conceivable cyclization of the δ-hydroxy ester system, with expulsion of methanol, is sterically feasible. But this geometrical impediment to lactonization (e.g., to IV) is removed in (one epimer of) the carbinolamine in which the allylic C-N bond has been broken by hydrogenolysis. Catalytic reduction of echitamine with platinum in ethanol gave in high yield, without further treatment, a lactone, m.p. 140 - 144° (from ether), m.p. 154 - 157° (from benzene) (Found: C, 71.25; H, 7.46; N, 7.96; C-Me, 5.74; OMe, 0.16. $C_{21}H_{26}O_3N_2$ requires: C, 71.16; H, 7.39; N, 7.90; two C-Me, 8.48; OMe, 0.00.) after the absorption of one mole of hydrogen. The properties of this reduction



V



VI

[11] F. A. L. Anet, A. S. Bailey and R. Robinson, Chem. & Ind. 944 (1953).

product,[12] for which we adopt the denomination <u>echitinolide</u>, are indeed fully consonant with the expression (IV). The NMR spectrum is characterized by the absence of any O-methyl peak near $\tau = 6.3$, but the following features are readily distinguished: N-methyl (singlet at 7.53), C-methyl (broader singlet at 7.76) and a second C-methyl (doublet at 8.48; J = 6.6 cps). The infrared spectrum includes sharp OH and NH maxima, as well as a carbonyl peak at 1742 cm^{-1}, increasing to 1754 in the O-monoacetate, m.p. 210 - 214°, (Found: C, 70.03; H, 7.30; N, 7.27. $C_{23}H_{28}O_4N_2$ requires: C, 69.67; H, 7.12; N, 7.07.) (sharp NH but no OH infrared peak) obtained with acetic anhydride-pyridine under mild conditions. The much lower pK_a (5.4; 60% ethanol) of IV is consistent with the proximity of acyloxy and tertiary amino functions.

An isomer, isoechitinolide (V), m.p. 149 - 154° (from ether) (Found: C, 70.89; H, 7.15; N, 7.90), with ν_{max} 1754 cm^{-1}, containing no hydroxyl and no double bond, is formed when IV is heated with hydrochloric acid. Probably the <u>sec</u>-butenyl residue epimerizes prior to ring closure; with the intact system (II) the corresponding cyclization can be shown to be sterically completely prohibited, and we note that echitamine chloride is entirely stable to aqueous acid under these conditions.

Echitamine shows ultraviolet absorption almost identical with that of echitamine chloride [$\lambda\lambda_{max}$ 235 mμ (3.93); 295 mμ (3.55)], even in strongly alkaline solution, where any basic ionization is repressed. The α-methiodide

---

[12] Echitinolide may well be and probably is identical with 'dihydroechitamine' (ref. 4; no m.p. or analytical data reported) and in this event the latter has been incorrectly formulated as $C_{22}H_{28}O_3N_2$. We prefer to reserve the name dihydroechitamine for the derivative otherwise identical with echitamine but with ethyl in place of ethylidene. Very probably echitinolide is also identical with 'base B' of ref. 3, also then incorrectly formulated.

gives a very similar spectrum, if allowance is made for the absorption of iodide ion. Echitinolide (IV) absorbs at longer wavelengths [$\lambda\lambda_{max}$ 248 mμ (3.91); 309 mμ (3.55)] as does isoechitinolide (V), but acidification of the solution causes downward displacement of the maxima in each case. Some of the previous authors (refs. 2 - 4) have sought to identify the hypsochromic shift in acid with the accumulation of positive charge on N_b in an eserine-like system[13] (N_a-C-N_b); this suggestion is notable in its failure to extend to the parent substance, echitamine, uncharged but with the same 'shifted' spectrum. We believe it to be more than coincidental that all of the compounds with low wavelength absorption have N_a equatorial (with respect to the six-membered carbocyclic ring C), on the basis of the structures proposed, while absorption appearing above 240 mμ (and above 300 mμ) can be consistently correlated with structures in which N_a has an axial conformation. Thus the cation of IV may exist in an open form, as in VI, with equatorial N_a, and this view is supported by the infrared spectrum of echitinolide hydrochloride, with characteristic broad carboxylic hydroxyl absorption at 2860 - 3450 cm^{-1}.

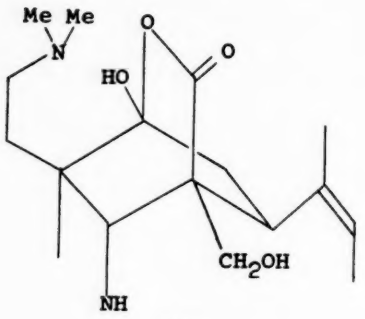
The methine[4,14] obtained in the 'facile Hofmann degradation' with echitinolide ('dihydroechitamine')[12] methiodide, should be VII, and the empirical formula of this methine must then be revised from $C_{23}H_{32}O_4N_2$ to $C_{22}H_{30}O_4N_2$. The zinc-hydrochloric acid reduction product, 'deoxy<u>neo</u>dihydroechitamine-methine'[4], is still a lactone, with structure (VIII); there is

---

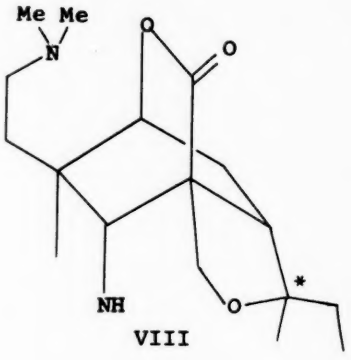
[13] Cf. H. F. Hodson and G. F. Smith, <u>J. Chem. Soc.</u> 1877 (1957).

[14] This 'dihydroechitamine-methine' was originally described as a 2-hydroxyindoline (ref. 4). The chemical literature contains no authenticated example of an N-unsubstituted 2-indolinol and we think it unlikely that any such system would be capable of existence independently of the corresponding indolenine.

now no opportunity for conformational inversion in the conjugate acid, so the ultraviolet spectrum [$\lambda\lambda_{max}$ 247 mμ (3.97); 307 mμ (3.59)] of this derivative is unchanged in acidic solution.[15]



VII



VIII

The zinc dust and selenium degradations leading to echitamyrine[4] and the dimethylpyrrolo(2′:3′-3:4)quinoline[3] might proceed via the intermediate (IX), which could arise from the iminium cation (VI) of IV by 1,2 migration of the indoline α carbon. We suggest that the specific biogenetic derivation og echitamine involves the precursor (X) in Mannich cyclization; the species (X) differs only in the most trivial sense from one already considered to account for the formation of the alkaloid gelsemine.[16] A close relationship to the quaternary alkaloid C-fluorocurarine[17] is apparent, while the system

---

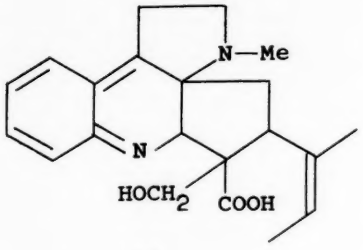
* No configurational representation at the starred atom intended.

[15] N_a appears never to be protonated in these acidic solutions, probably because of steric hindrance to solvation of the ion; the steric block is also responsible for the unusual difficulty of N_a-acetylation of many of these derivatives.

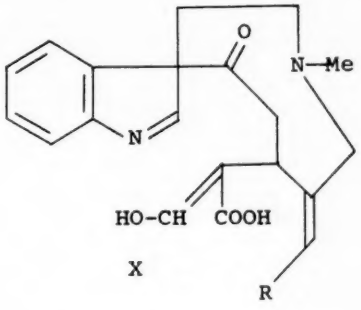
[16] H.Conroy and J.K. Chakrabarti, Tetrahedron Letters No. 4, 6 (1959).

[17] W. von Philipsborn, K. Bernauer, H. Schmid and P. Karrer, Helv. Chim. Acta 42, 461 (1959) and earlier references cited.

not cyclized, but retaining the carboxyl residue, is found in the alkaloids corynoxeine and rhyncophylline.[18,19]



IX



X

Acknowledgments - This research is supported by generous grants from the National Science Foundation (NSF-G6586) and from the National Institutes of Health (RG-6190C1 and CY-3722C1). Microanalyses are by Dr. S. M. Nagy (M. I. T.) and the Schwarzkopf Microanalytical Laboratory. We are greatly indebted to Dr. D. Dickel of CIBA (Summit) for the preparation of the echitamine.

---

[18] N. An Cu, R. Goutarel and M.-M. Janot, Bull. Soc. Chim. Fr. 1292 (1957).

[19] J. C. Seaton and L. Marion, Canad. J. Chem. 35, 1102 (1957).

Tetrahedron Letters No. 6, 10-12, 1960. Pergamon Press Ltd. Printed in Great Britain.

NITROGEN GLYCOSIDES. N-GLUCOSYL DERIVATIVES OF SUBSTITUTED RHODANINES

R. Bognár and W. Wieniawski

Institute of Organic Chemistry, L. Kossuth University,

Debrecen, Hungary

(Received 8 February 1960)

GLUCOSYL derivatives of rhodanine and substitutes rhodanines have not been reported in the Literature. These compounds appear to be of significance both from the physiological and chemical points of view. It is generally known that several compounds containing the thiazoline, thiazolidine, or thiazolidine-thione(2)-one(4), i.e. rhodanine ring are physiologically active; the bacteriostatic, fungistatic and other pharmacological and toxicological activities of the rhodanine derivatives have been investigated recently.[1] Chemically, the chief interest lies in the tautomerism of the rhodanine ring: if it forms glycosyl derivatives what is the exact structure

[1] F.C. Brown et al., J. Amer. Chem. Soc. 78, 384 (1956); W.M.McLamore et al., Ibid. 75, 105 (1953); M. Janewiec et al., Bull. Acad. Pol. Sci. Cl. VI, 5, 201 (1957). W. Wieniawski et al., Roczn. Chem. 32, 545 (1958); C.R. Bradsher and F.C. Brown, Nature, Lond. 168, 17 (1951) J. Amer. Chem. Soc. 76, 114 (1954); G.J.M. van der Kerk et al., Mededel. Landbouwhogeschool Gent 18, 402 (1953); Chem. Abstr. 48, 316 (1953); S.A. Tavab and A. Mustafa et al., Nature, Lond. 183, 607 (1959); F.J. Allan, G.G. Allan and C.F.M. McNeil, Nature, Lond. 184, 1637 (1959).

of these compounds?

We have found that rhodanine derivatives containing exocyclic double bend in position 5 give crystalline tetraacetyl-glucosyl-derivatives with acetobromo-glucose in aqueous acetone in the presence of sodium hydroxide.

We have prepared the following compounds in this way:

N-(tetraacetyl-D-glucosyl)-5-benzalrhodanine (I), bright yellow needles from methanol (yield 57%); m.p. 193 - 194°; $[\alpha]_D^{20} = -171^\circ$ (c=1, in Py), U.V. spectrum, λ_{max} in mμ (log ε): 280 (4.02); 374 (4.46). (Found C, 51.8; H, 4.7; N, 2.4; S, 11.3; acetyl, 29.9%; Calc. for $C_{22}H_{25}O_{10}NS_2$ C, 52.3; H, 4.6; N, 2.5; S, 11.6; acetyl, 31.1%.)

N-(tetraacetyl-D-glucosyl)-5-anisalrhodanine (II), bright yellow needles from chloroform-methanol, and from acetone. (Yield 56%) m.p. 226 - 228°. $[\alpha]_D^{20} = -181^\circ$ (c=1, in Py); U.V. spectrum, λ_{max} in mμ (log ε γ: 245 (3.89), 295 (4.17), 391 (4.65). (Found: N, 2.6; Calc. for $C_{26}H_{27}O_{11}NS_2$; N, 2.4%).

N-(tetraacetyl-D-glucosyl)-5-isopropylidene rhodanine (III), pale yellow needles from methanol (yield: 40%); m.p.: 193 - 195°; $[\alpha]_D^{20} = -99^\circ$ (c=1, in Py). U.V. spectrum: λ_{max} in mμ, (log ε): 270 (3.92); 345 (4.44). Found: C, 47.3; H, 5.0; N, 3.0; S, 12.9; acetyl, 34.9; (Calc. for $C_{20}H_{25}O_{10}NS_2$: C, 47.7; H, 5.0; N, 2.8; S, 12.7; acetyl, 34.2%)

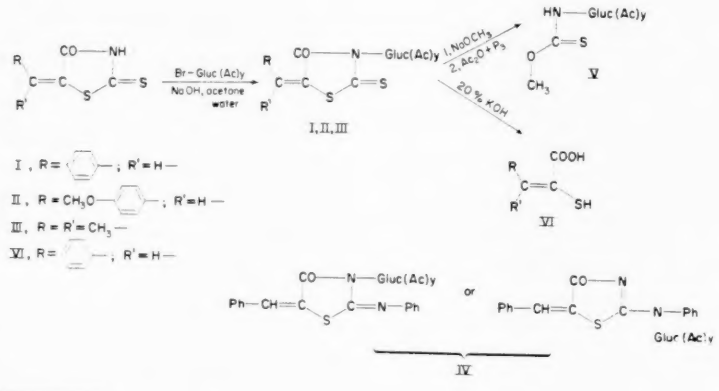
N-(tetraacetyl-D-glucosyl)-5-benzal-2-phenylamine-thiazolidene-(4) (IV), yellow needles from methanol-water, (yield 42%). m.p.: 203 - 204°; $[\alpha]_D^{20} = -76^\circ$ (c=1, in Py) U.V. spectrum λ_{max} in mμ (log ε): 230 (4.19); 336 4.34). (Found: C, 59.1; H, 5.1; N, 4.6; S, 5.1; acetyl, 28.0; Calc. for $C_{30}H_{30}O_{10}N_2S$: C, 59.0; H, 5.0; N, 4.6; S, 5.3; acetyl, 28.2%).

The following experiments and degradation products prove the structure of (I), (II) and (III). We have ascertained the intact thione group in the

tetraacetyl-glucosyl-derivatives; the N-alkyl-rhodanines did not react with acetobromo-glucose; β-phenyl-α-thiel-acrylic acid (V) was formed from (I) by alkaline degradation with 10% potassium hydroxide; our conclusive proof that these compounds are N-glycosyl derivatives: by methanolysis of (I) and (II) with sodium methylate in abs. methanol followed by acetylation of the amorphous product we have obtained N-(tetraacetyl-D-glucosyl)-methylcarbamate (VI), which was identified with an authentic[2] sample.

It is to be noted that the reaction of rhodanine and acetobromo-glucose in aqueous acetone in the presence of sodium hydroxide gave only (III) and no glucosyl derivative of the unsubstituted rhodanine could be obtained in this way.

The structure of (IV) has not yet been proved. In our opinion, of the possible tautomeric forms there are two N-glucosyl structures which ought to be taken into consideration.[3]



[2] A. Müller and A. Wilhelms, Ber. 74, 698 (1941).

[3] F.B. Dains et al., Univ. Kansas Sci. Bull. 24, 15 (1936), Chem. Abstr. 32, 3396 (1936).

Tetrahedron Letters No. 6, pp.13-16, 1960. Pergamon Press Ltd. Printed in Great Britain.

SECONDARY ISOTOPE EFFECTS AND MASS-SENSITIVE AMPLITUDES OF VIBRATION

L. S. Bartell

Department of Chemistry, Iowa State University, Ames, Iowa

(Received 29 January 1960)

In recent years secondary isotope effects in reactions involving carbonium ion transition states have been explored intensively by Lewis, Shiner, and others.[2] The retardation accompanying deuterium substitution at β carbons is almost universally attributed to a hyperconjugative weakening of C-H or C-D bonds on the β carbon atoms. The retardation associated with α substitution, on the other hand, is acknowledged to be entirely unrelated to hyperconjugation, and hence unrelated to the β effect. It is the purpose of this communication to point out a factor, heretofore neglected, which seems to account for a substantial part of the β effect without requiring that C-H bonds be weakened in the transition state. Further, it bridges the gap between the α and β effects as it can be shown, in the α effect, to reduce essentially to the accepted explanation of Streitwieser et al.[3]

---

[1] Research supported by the National Science Foundation.

[2] For reviews see E. S. Lewis, Tetrahedron 5, 143 (1958); V. J. Shiner, Tetrahedron 5, 243 (1958).

[3] Streitwieser, Jagow, Fahey and Suzaki, J. Amer. Chem. Soc. 80, 2326 (1958).

The principle of the proposed argument is that the amplitudes of vibration of hydrogen atoms are larger than the amplitudes of the heavier deuterium atoms by a readily predictable amount. Nonbonded repulsions, averaged over the atomic vibrations, are greater for hydrogen atoms than deuterium atoms since, in the range of interest, the second derivative of the nonbonded potential function is positive. Moreover, there are more, and stronger nonbonded repulsions in the crowded tetrahedral reactant than in the carbonium ion transition state. Accordingly, the trigonal transition state is relieved of nonbonded repulsions to a greater extent when it contains hydrogen than when it contains deuterium. For a given nonbonded interaction the isotope effect is proportional to the mean-square of the mass-sensitive component of the relevant amplitude of vibration and to the second derivative of the potential function. Recent determinations of amplitudes from spectroscopic and electron diffraction data coupled with potential functions proposed elsewhere,[4] make it possible to estimate the numerical magnitude to be expected.

In preliminary calculations, for simplicity, the interactions of the solvent molecules and leaving group with the carbonium ion were ignored in the transition state. Unfortunately, the lack of structural data for the molecules considered made it necessary to resort to guesses. In the case of tosylate solvolyses the calculated isotope effect was found to be exceedingly sensitive to the assumed molecular configurations, and the

---

[4] L. S. Bartell, J. Chem. Phys. (in press).

values calculated ranged from rather less than the observed value to considerably more. For the solvolysis of t-amyl chloride the calculated $\Delta\Delta E_a$ was roughly half the observed $\Delta\Delta F_a^2$. In the analogous gas phase equilibrium[5]

$$Me_3B{:}NMe_3 = BMe_3 + NMe_3$$

where the structures of the molecules are much less speculative than in solvolysis reactions, the calculated isotope effect was approximately equal to the observed value. It is not possible to assess the accuracy of the assumed parameters at present. Nevertheless it is clear that the magnitude of the nonbonded effect is entirely comparable with that of the observed isotope effect. Therefore it would be injudicious to interpret isotope effects solely on the basis of hyperconjugation.

It is fitting to observe that nonbonded interactions obscure the role of hyperconjugation not only in studies of isotope effects, but also in studies of bond lengths and heats of formation of molecules in the ground state. According to evidence recently elicited,[4] nonbonded repulsions of the magnitude observed in Urey-Bradley analyses of vibrational spectra[6] are sufficient to account for variations of bond lengths and energies that are usually attributed to hyperconjugation and hybridization changes.

---

[5] Love, Taft and Wartik, Tetrahedron 5, 116 (1959).

[6] T. Simanouti, J. Chem. Phys. 17, 245 (1949); J. W. Linnett, ibid 17, 801 (1949).

The Urey-Bradley analyses also indicate that nonbonded repulsions account for a substantial part of the potential energy of bond bending. To the extent that hydrogen atoms can be considered to be moving in harmonic nonbonded potential wells in bending motions, the present model can be reduced to Streitwieser's model for the α isotope effect. Calculations based on experimental amplitudes of vibration and the potential parameters of references (4) and (6) agree in magnitude with those of Streitwieser based on observed vibrational frequencies.[3]

Many implications broader than the present correlations are suggested by the nonbonded model. Discussions of kinetic isotope effects other than α or β effects, and predictions of effects in rotational isomerization energies of hydrocarbons, spectra, and other observables will be presented along with the details of the present calculations in a forthcoming article.

Tetrahedron Letters No. 6, pp. 17-19, 1960. Pergamon Press Ltd. Printed in Great Britain.

THE STRUCTURE OF HCN TETRAMER

Bruce R. Penfold and William N. Lipscomb

Department of Chemistry, Harvard University

Cambridge 38, Massachusetts

(Received 15 February 1960)

1960

Recently, Wadsten and Andersson[1] have proposed that the polymerisation product of hydrogen cyanide, generally regarded as the tetramer, is in fact the dimer, "iminoacetonitrile". Their evidence was obtained from a preliminary X-ray diffraction study of single crystals and from infra-red absorption measurements.

Webb, Frank and Schneider[2] had previously summarized chemical evidence for the molecular structure and presented the results of their own infra-red and ultra-violet absorption measurements and dipole moment measurements. Their deductions were that the compound is diaminomaleonitrile in the solid state and in dilute solution. Sass and Donohue[3]

---

[1] T. Wadsten and S. Andersson, Acta Chem. Scand. 13, 1069 (1959).

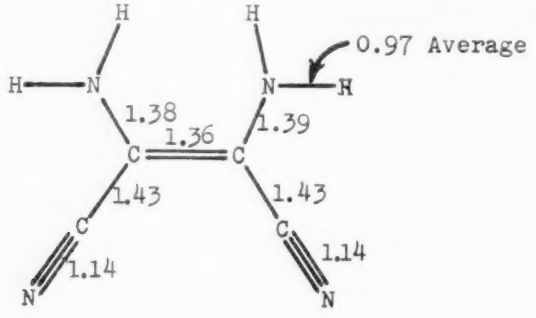
[2] R. L. Webb, S. Frank and W. C. Schneider, J. Amer. Chem. Soc. 77, 3491 (1955).

[3] R. L. Sass and J. Donohue, Acta Cryst. 10, 375 (1957).

first reported the unit cell constants and space group of the crystalline solid but did not determine the crystal structure.

We wish to report that, as a result of a detailed structure analysis of single crystals by X-ray diffraction, we have conclusive proof that the compound in question is indeed the tetramer of HCN and is diaminomaleonitrile in the solid state. The crystals used in our study were kindly supplied by Mr. J. Vaughan, Chemistry Department, University of Canterbury, New Zealand. They have the same unit cell dimensions as those examined by Sass and Donohue[3] and by Wadsten and Andersson.[1] The measured density was 1.37 g/cc.

Following a three dimensional least squares refinement of atomic parameters, in which about 900 independent X-ray reflections were considered, the positions of all the atoms are known with standard errors or 0.003 Å for carbons and nitrogens and 0.05 Å for hydrogens. The value of the reliability factor R is 0.08 for all observed reflections. The carbon nitrogen skeleton of the molecule is planar and the bond lengths are as shown in the figure below.



1960

The crystal structure was solved by the application of Patterson superposition techniques involving the use of the Buerger minimum function[4] in three dimensions. Location of single interatomic vectors was made possible by a novel form of modification of the Patterson function as described by Jacobson, Wunderlich and Lipscomb.[5] Details of the structure analysis will be reported elsewhere.

The appointment of B. R. Penfold was supported by the International Cooperation Administration under the visiting Research Scientists Program administered by the National Academy of Sciences of the United States of America. We also wish to thank the National Institutes of Health and the Air Force Office of Scientific Research for financial support.

---

[4] M. J. Buerger, Vector Space. J. Wiley and Sons, New York (1959).

[5] R. A. Jacobson, J. A. Wunderlich and W. N. Lipscomb, Nature, London 184, 1719 (1959).

Tetrahedron Letters No. 6, pp. 20-22, 1960. Pergamon Press Ltd.
Printed in Great Britain.

OXIDATION OF ORGANIC SULPHIDES WITH OPTICALLY ACTIVE PEROXY ACIDS. ASYMMETRIC SYNTHESIS OF SULPHOXIDES

K. Balenović, N. Bregant, and D. Francetić

Chemical Laboratory, Faculty of Science, University of Zagreb, Strossmayerov trg 14, Zagreb, Yugoslavia

(Received 20 January 1960; in revised form 15 February 1960)

THE resolution of m-carboxyphenylmethylsulphoxide (I, R=H) has confirmed the fact that sulphoxides may exist in optically active forms[1], and indicates the tetrahedral structure of these compounds.

We have found at present that methyl m-methylthiobenzoate (II) oxidised with percamphoric acid showing $[\alpha]_D$ +52°[2] in ether at 0° gave m-carbomethoxyphenylmethylsulphoxide (I, R=CH_3) in a 74% yield with the

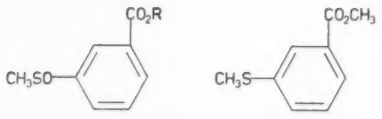
---

[1] P.W.B. Harrison, J. Kenyon, and H. Phillips, J. Chem. Soc. 2079 (1926).

[2] N.A. Milas and A. McAlevy, J. Amer. Chem. Soc. 55, 349 (1933).

b.p. 80-90°/0.02 mm. (bath temp.) and $[\alpha]_D$ +2.2° ± 0.2° (c, 2.88 in methanol) (Found: C, 54.88; H, 5.29. $C_9H_{10}O_3S$ requires: C, 54.53; H, 5.09).

1960



I II

Hydrolysis of compound I (R=CH_3) in an equimolar amount of diluted aqueous sodium hydroxide afforded m-carboxyphenylmethylsulphoxide (I, R=H) in a 80% yield, m.p. 168°, and showing $[\alpha]_D$ +1.4° (in methanol). Fractional crystallisation from chloroform - petroleum ether gave the same compound with the m.p. 170° and $[\alpha]_D$ +5.3° ± 0.2° (c, 1.960 in methanol) (Found: C, 51.78; H, 4.38. Calc. for $C_8H_8O_3S$: C, 52.16; H, 4.38).

Analogous oxidation of methyl m-ethylthiobenzoate gave m-carbomethoxyphenylethylsulphoxide with the m.p. 100-105°/0.01 mm. and $[\alpha]_D$ +2.5° ± 0.2° (c, 2.225 in methanol) (Found: C, 56.74; H, 5.85. $C_{10}H_{12}O_3S$ requires: C, 56.58; H, 5.69).

Hydrolysis of the above compound afforded m-carboxy-

phenylethylsulphoxide[3], showing the m.p. 104° and $[\alpha]_D$ +1.4° ± 0.2° (c, 3.410 in methanol) (Found: C, 54.38; H, 5.25. Calc. for $C_9H_{10}O_3S$: C, 54.54; H, 5.09).

In all these oxidations with percamphoric acid the water - soluble sulphoxide was easily separated from the ether - soluble camphoric acid. In separate runs it was found that our sulphoxide was completely free of either camphoric or percamphoric acid.

The significance of these results for the determination of the absolute configuration of sulphoxides will be given in due course.

---

[3] J. Holloway, J. Kenyon, and H. Phillips, J. Chem. Soc. 3000 (1928).

Tetrahedron Letters No. 6, pp. 23-29, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

AN LCAO TREATMENT OF THE ACIDITY OF HYDROCARBONS[1]

Andrew Streitwieser, Jr.[2]

Department of Chemistry, University of California

Berkeley, California

(Received 5 February 1960)

EARLY in the development of the simple molecular orbital theory of organic chemistry, Wheland[3] showed that the theory qualitatively accounts for the acidities of hydrocarbons. The more quantitative experimental pK values of McEwen[4] were not available at that time. It is important to determine the extent to which simple MO theory quantitatively correlates not only McEwen's values but also the acidities of some hydrocarbons of recent interest, for example, the rather acidic fluoradene, I, recently prepared by Rapoport and Smolinsky.[5]

---

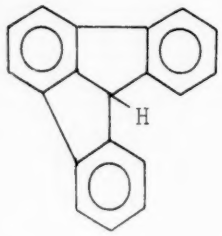
[1] This work was supported by the United States Air Force through the Air Force Office of Scientific Research of the Air Research and Development Command, under Contract No. AF-49(638)-105. Reproduction in whole or in part is permitted for any purpose of the United States Government.

[2] Alfred P. Sloan Fellow; National Science Foundation Science Faculty Fellow, 1959-1960.

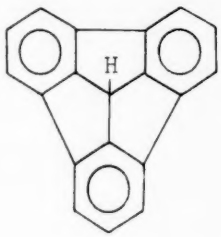
[3] G. W. Wheland, J. Chem. Phys. 2, 474 (1934).

[4] W. K. McEwen, J. Am. Chem. Soc. 58, 1124 (1936).

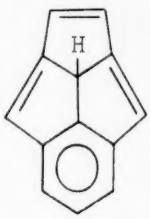
[5] H. Rapoport and G. Smolinsky, ibid. 80, 2910 (1958).



I

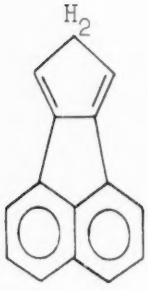


II

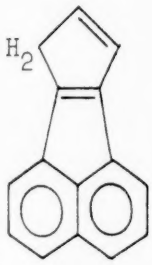


III

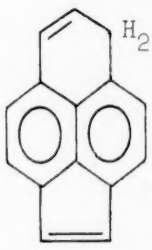
IV



V



VI



VII

Following Wheland,[3] we assume that the acidity of the hydrocarbon is proportional to the change in the π-bond energy resulting from the difference in conjugation between the hydrocarbon, AH_i, and the corresponding anion, A_i^-. We use the usual form of the simple MO theory with neglect of overlap and with all β's equal. The π-energy of a compound with n π-electrons then takes the form, $E_\pi = n\alpha + M\beta$, in which α is the usual Coulomb integral. Hence:

$$\Delta E_{\pi_i} = (E_\pi)_{A_i^-} - (E_\pi)_{AH_i} = 2\alpha + \Delta M_i \beta$$

We assume, with Wheland, that effects such as changes in σ-bond energies and solvation are relatively constant from one system to another. Note also that hyperconjugation effects in the hydrocarbon are neglected. We also assume that any strain energy is the same in the hydrocarbon and in the anion.

Wheland assigned a value to β derived from empirical resonance energies. There is reason to suspect this procedure and instead we retain β as an adjustable parameter. The correlation takes the following form, in which the empirical slope, b, contains β:

$$pK_i = a + b\Delta M_i$$

ΔM values and McEwen's pK's for a number of hydrocarbons are summarized in Table I and are plotted in Figure 1. In the scatter of points a good straight line emerges through the three compounds whose anions are expected to be completely coplanar, an assumption implicit in taking all β's equal. The anions of the other compounds contain aryl groups which may be expected to deviate substantially from coplanarity; they are less acidic than predicted by the correlation by about 4 pK units per nonplanar phenyl group, an amount which may be shown to correspond to an angle of twist of roughly 30-40°.

It is unfortunate that the data for planar carbanions is so limited; nevertheless, since the deviations found are in the right direction and are of reasonable magnitude, the correlation should be considered to be successful. Furthermore, we can account very well for the rather more qualitative information

TABLE 1. Acidities of Hydrocarbons

Compound	ΔM	pK Expl.[a]	pK Calcd.
Indene	1.747	21	
9-Phenylfluorene	1.980	21	
Fluorene	1.523	25	
Diphenyl-p-biphenylylmethane	1.819	31	
Triphenylmethane	1.800	33	
Diphenylmethane	1.301	35	
Toluene	0.721	37[b]	
Cycloheptatriene	1.110	>25[c]	31
Perinaphthene	1.697	16-25[c]	22
Cyclopentadiene	2.000	16-20[c]	17
Fluoradene, I	2.115	11,[d] 13.5[e]	15
Cyclopropene	0		~48
1,2,3-Triphenyl-cyclopropene	1.301		28
4,5-Methylenephenanthrene	1.514[f]		25
II	2.225		14
III	2.189		14.5
IV	2.411		11
V	2.024		17
VI	1.911		18.5
VII	1.964		18

[a] Ref. 4 unless indicated otherwise.
[b] Estimated from cumene.
[c] See text.
[d] In water.
[e] In 97% aqueous methanol.
[f] Experiments with this compound are currently in progress.

1960

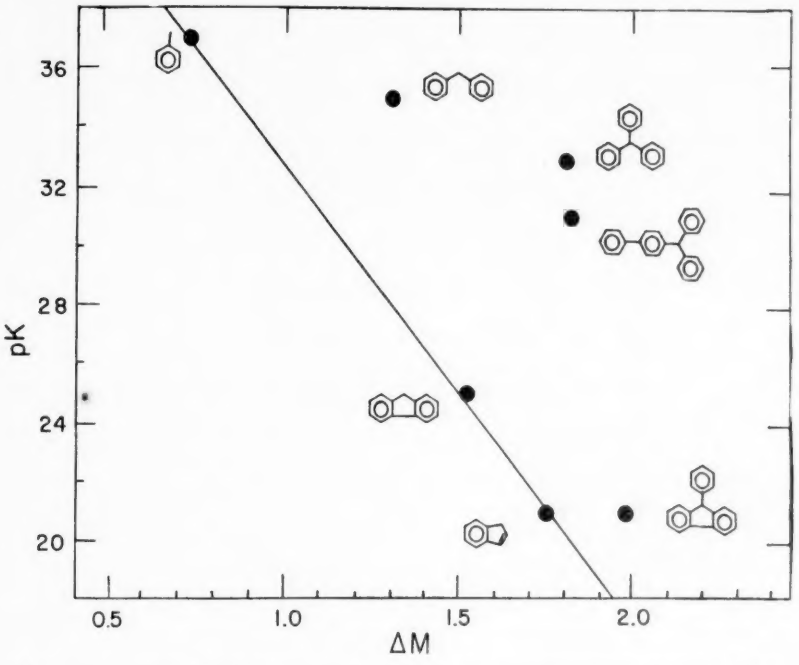


Fig. 1. Correlation of Acidities of Hydrocarbons with Simple MO Calculations

available for several other hydrocarbons. Cycloheptatriene does not condense with ketones or with ethyl oxalate with refluxing alcoholic sodium ethoxide, conditions under which fluorene condenses readily.[6] Hence, cycloheptatriene is less acidic than fluorene in agreement with the calculations. In acidity, perinaphthene apparently lies between cyclopentadiene and fluorene,[7] in agreement with its calculated pK of 22.

---

[6] J. Thiele, Ann. 319, 226 (1900); Ber. 33, 851 (1900).

[7] V. Boekelheide and C. E. Larrabee, J. Am. Chem. Soc. 72, 1245 (1950).

Cyclopentadiene reacts with potassium in benzene in the cold, conditions under which indene is inert; cyclopentadienylpotassium is reported to be decomposed by water.[8] Accordingly, the pK of cyclopentadiene probably lies between 16 and 20, in agreement with the calculated value, 17.

The correlation predicts the pK of fluoradene to be 15 in comparison with the experimental value, 11-13.5.[5] Most of McEwen's values are based on experiments in ether or benzene solution but refer to methanol in water, whereas the fluoradene values refer to water and aqueous methanol. The calculated results are not corrected for any effects of solvation. The agreement is good; McEwen's values are not better than ± 1 pK unit.

In Table 1, we predict the acidities of several known and unknown hydrocarbons of theoretical interest. In all of these results, the anion-stabilizing character of the five-membered ring is clearly in evidence. The stability of the cyclopentadienyl anion persists even when this ring system is but a part of a more complex structure. Note, for example, that the introduction of a vinyl bridge in perinaphthene, giving compound VII, results in a calculated decrease of 4 pK units.

Although energies for some of these compounds have been reported previously, in most cases new calculations were made usually with an IBM 701 computer and programs previously

---

[8] J. Thiele, Ber. 34, 68 (1901).

discussed.[9] Energies and coefficients for the molecular orbitals and bond orders for many of the compounds described in this paper have been prepared as a separate appendix.[10]

I am indebted to Dr. P. M. Nair, Dr. R. B. Williams, Mr. J. B. Bush and Mr. J. I. Brauman for technical assistance.

1960

---

[9] A. Streitwieser, Jr. and P. M. Nair, Tetrahedron 5, 149 (1959).

[10] Material supplementary to this article has been deposited as Document number 6229 with the ADI Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington 25, D.C. A copy may be secured by citing the Document number and by remitting $2.50 for photoprints, or $1.75 for 35 mm. microfilm. Advance payment is required. Make checks or money orders payable to: Chief, Photoduplication Service, Library of Congress.

Tetrahedron Letters No. 6, pp. 30-34, 1960. Pergamon Press Ltd. Printed in Great Britain.

SYNTHESIS OF CONDENSED THIOPHENES, DIARYLS AND DIALKYLS THROUGH ARYLLITHIUM AND ALKYLLITHIUM DERIVATIVES

V. N. Gogte, V. S. Palkar and B. D. Tilak

Department of Chemical Technology,

University of Bombay, Bombay

(Received 15 February 1960)

A FEW condensed thiophenes have been synthesised by the cyclization of diaryl sulphides by the action of arylsodium and/or aryllithium derivatives,[1,2] and by the action of sodamide on diaryl sulphoxides.[3,4] In view of the formation of diphenyl sulphone-2:2'-dilithium[5,6] (II) from diphenyl sulphone (I), and the synthesis of 2:2'-and 3:3'-dithionaphthenyls by the action of anhydrous cupric chloride on the corresponding Grignard reagents achieved earlier by us,[7] the cyclization of (I) by interaction of its dilithium

---

1 A. Luttringhaus, G. Wagner-v.saaf, E. Sucker and G. Borth, Liebigs Ann. 557, 46 (1947-48).

2 G. Wittig and E. Benz, Chem.Ber. 91, 873 (1958).

3 A. Schonberg, Ber. 56, 2275 (1923).

4 R. Wilputte and R.H. Martin, Bull.Soc.Chim.Belg. 65, 874 (1956).

5 H. Gilman and D.L. Esmay, J.Amer.Chem.Soc. 75, 278 (1953).

6 K. Oita and H. Gilman, J.Org.Chem. 22, 336 (1957).

7 L.J.Pandya, D.S. Rao and B.D. Tilak, J.Sci.Industr.Res.India 18B, 516 (1959).

derivative (II) with cupric chloride was investigated. It is of interest to record that dibenzothiophene (III) (20%) was formed along with the expected dibenzothiophene-5:5-dioxide (IV) (50%) (separation by chromatography over alumina using benzene as eluent). In later experiments, the mixture itself was reduced by treatment with lithium aluminium hydride, when (III) was obtained.

The above method which represents a new synthesis of condensed thiophenes from diaryl sulphones may prove to be of general interest for the preparation of other condensed thiophenes from diaryl sulphones. Thus the lithium derivative of 2:2'-dinaphthyl sulphone (V),[8] on treatment with anhydrous cupric chloride, gave a product which on treatment with lithium aluminium hydride gave dinaphtho-(2:1-b,1':2'-d)-thiophene (VI).

Conversion of diphenyl sulphoxide and diphenyl sulphide to (III) by the procedure was unsuccessful. In the case of diphenyl sulphoxide, interaction of butyllithium followed by treatment with anhydrous cupric chloride gave diphenyl sulphide. When diphenyl sulphide was treated with butyllithium or phenyllithium and then with cupric chloride, it remained unreacted.

When phenyllithium was treated with cupric chloride, diphenyl was obtained in nearly quantitative yield. Although a few diaryls and dialkyls have been prepared earlier by the interaction of the corresponding magnesium Grignard reagents with metal halides,[9-12] this method does not appear to have

---

[8] A.I. Vogel, Practical Organic Chemistry p. 551. Longmans, Green, London (1956).

[9] J. Kriezewsky and E.E. Turner, Trans. Chem. Soc. 559 (1919).

[10] H. Gilman and H.H. Parker, J.Amer.Chem.Soc. 46, 2823 (1924).

[11] J.H. Gardner and P. Borgstrom, J.Amer.Chem.Soc. 51, 3375 (1929).

TABLE 1

Synthesis of Condensed Thiophenes, Diaryls and Dialkyls

through Aryllithium and Alkyllithium Derivatives

Starting material	Reaction products, molecular formula, % yields.	m.p. or b.p.	Isolation and purification of reaction products	Analysis % Found C	H	S	Required C	H	S	Refs.
I	III, $C_{12}H_8S$ (70%)	m.p. 99°	Reduction with $LiAlH_4$, chromatography, distillation, crystallization; compared with an authentic sample.	78.2	4.3	17.2	78.3	4.4	17.4	5
V	VI, $C_{20}H_{12}S$ (50%)	m.p. 208-9°	Reduction with $LiAlH_4$, chromatography, crystallisation, compared with an authentic sample.							8,13,14.
PhBr	Diphenyl, $C_{12}H_{10}$ (100%)	m.p. 70-1° b.p. 95-130° (bath temp)/ 6 mm	Distillation, crystallization.							15
α-Bromo-naphthalene	1:1'-Dinaphthyl, $C_{20}H_{14}$ (18%)	m.p. 160-1°	Chromatography, distillation, crystallization.	94.2	5.7		94.5	5.5		16
	Naphthalene, $C_{10}H_8$ (31%)	m.p. 81°	Chromatography, distillation, crystallization.							
	Perylene, $C_{20}H_{12}$ (9%)	m.p. 275-7°	Chromatography, distillation, sublimation & crystallization.	95.5	4.4		95.2	4.8		17

Thionaphthene	2:2'-Dithionaphthenyl, $C_{16}H_{10}S_2$ (52%)					7
3-Iodothionaphthene	3:3'-Dithionaphthenyl, $C_{16}H_{10}S_2$ (11%)					7
n-C_4H_9Br	n-Octane, C_8H_{18} (22%)	b.p.121-3° (bath temp)	Fractional distillation.	83.6 15.1	84.2 15.8	18
n-$C_{12}H_{25}Cl$	Tetracosane, $C_{24}H_{50}$ (33%)	m.p.53-4°	Fractional distillation, crystallization.	84.8 14.8	85.2 14.8	19
n-$C_{18}H_{37}Cl$	Hexatriacontane, $C_{36}H_{74}$ (32%)	m.p.76° b.p.220-35° (bath temp)/ 0.-005 mm	Fractional distillation, crystallization.	85.9 14.2	85.4 14.6	
	Octadecane, $C_{18}H_{38}$ (32%)	b.p.89-91° (bath temp)/ 0.005 mm	Fractional distillation.	85.4 14.6	85.1 15.0	
	Octadecylalcohol, $C_{18}H_{37}OH$ (36%)	m.p.58.5-59.5° b.p.115-123° (bath temp)/ 0.005 mm	Fractional distillation, crystallization.	80.2 14.2	80.0 14.1	

13 B.D. Tilak, Proc.Indian Acad.Sci. 33A, 131 (1951).

14 K. Rabindran and B.D. Tilak, Proc.Indian Acad.Sci. 38A, 271 (1953).

15 R. Adams, Organic Reactions Vol VI, p. 353 (1951).

16 H. Gilman, E.A. Zoellner and W.M. Selby, J.Amer. Chem.Soc. 55, 1252 (1933).

17 H. Gilman and C.G. Brannen, J.Amer.Chem. Soc. 71, 657 (1949).

18 H. Gilman et al., J.Amer.Chem.Soc. 71, 1499 (1949).

19 R.N. Meals, J.Org.Chem. 9, 211 (1944).

been sufficiently exploited for the synthesis of these compounds. Symmetrical diaryls and dialkyls have now been synthesised by the interaction of aryllithium and alkyllithium derivatives with anhydrous cupric chloride and the results are summarised in Table 1, which also includes analytical data. Where the figures of analysis are not quoted, the products were identified by comparison with authentic specimens. The table also includes 2:2'- and 3:3'-dithionaphthenyls as examples of the present synthesis.

When octadecyl chloride was treated with lithium alone the yield of hexatriacontane was lower (7%) than when the lithium derivative was treated with cupric chloride when the hydrocarbon was obtained in 32% yield. By-products which often accompany diaryls and dialkyls consist of the corresponding hydrocarbons and in the case of dialkyls, the corresponding alcohols are also formed in some cases.

Application of this method for the synthesis of other compounds of the above and other types will form the subject of further communications. It is hoped that a full account of the work will be published shortly in Tetrahedron.

---

[12] H. Gilman and M. Lichenwalter, J.Amer.Chem.Soc. 61, 957 (1939).

1960

196

Tetrahedron Letters. No. 7, pp. 1-3, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

THE BIOSYNTHESIS OF THE ERGOT ALKALOIDS

A. J. Birch, B. J. McLoughlin and Herchel Smith

Department of Chemistry, The University, Manchester

(Received 22 February 1960)

TRYPTOPHAN[1,2] has been implicated as a precursor in the biosynthesis of the ergot alkaloids including lysergic acid (I), agroclavine (II; R=H), and elymoclavine (II; R=OH). We[3] recently suggested that the remaining five carbon atoms [cf.(I)] in this group of substances arise from **mevalonic** acid. **Others**[1] have expressed similar views.

We have now grown a Claviceps purpurea species[4] on media containing, in turn, (2-^{14}C)-mevalonic lactone, $CH_3{}^{14}CO_2Na$ and $^{14}CH_3CO_2Na$, and have found radioactivity to be incorporated in each case into the resulting agroclavine and elymoclavine. Kuhn - Roth oxidation of the labelled agroclavine gave acetic acid derived from the 8- and 17-positions of the alkaloid. Reduction of the labelled **elymoclavine** with sodium in boiling isopropyl

TL 74

---

1 K. Mothes, F. Weygand, D. Groger and H. Grisebach, Z.Naturf.136, 41 (1958).

2 W.A. Taber and L.C. Vining, Chem. & Ind. 1218 (1959).

3 A.J. Birch and Herchel Smith, CIBA Foundation Symposium on Amino Acids and Peptides with Antimetabolic Activity (Edited by Wolstenholme and O'Connor) p. 247. J. and A. Churchill, London (1958).

4 A. Hofmann, R. Brunner, H. Kobel and A. Brack, Helv.Chim.Acta 40, 1358 (1957).

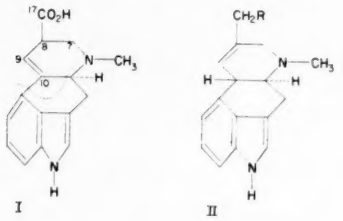
alcohol, and Kuhn - Roth oxidation of the product, gave acetic acid, presumably derived from the same two positions. Degradation of the acetic acid has in each case given the labelling on the individual carbon atoms. Radiochemical incorporations and the relative molar activities of the alkaloid and the samples of barium carbonate derived from the 8- and 17-positions are tabulated below.

Substrate	Agroclavine	Incorporation (%)	$BaCO_3(C_{17})$	$BaCO_3(C_8)$
(2-^{14}C)-mevalonic lactone	16,300	1.0	5060	0
$CH_3{}^{14}CO_2Na$	30,200	0.43	0	16,570
$^{14}CH_3CO_2Na$	59,850	0.83	5750	470

Substrate	Elymoclavine	Incorporation (%)	$BaCO_3(C_{17})$	$BaCO_3(C_8)$
(2-^{14}C)-mevalonic lactone	91,070	1.4	80,020	0
$CH_3{}^{14}CO_2Na$	82,950	1.0	0	37,980
$^{14}CH_3CO_2Na$	80,650	2.1	22,000	1780

Assuming the normal mode of incorporation of the substrates into terpenoid substances, we would expect radioactivity from (2-^{14}C)-mevalonic lactone to be incorporated only into the 7- or 17-positions, or possibly both. Likewise, we would expect radioactivity to be incorporated from $CH_3{}^{14}CO_2Na$ into the 8- and 10-positions, and from $^{14}CH_3CO_2Na$ mainly, if not solely, into the 9-, 16-, and 17-positions in the C_5-unit. The results above are fully

consistent with, although they do not prove, the presence of a terpenoid fragment in the two alkaloids.



I II

We thank the Department of Scientific and Industrial Research for a maintenance grant and Dr. J. Renz, Sandoz, Basel, for generously providing cultures of the Claviceps purpurea species and unlabelled alkaloids.

1960

TL 7A+

Tetrahedron Letters No. 7, pp. 4-8, 1960. Pergamon Press Ltd. Printed in Great Britain.

EIN ZWEIFACH ÜBERBRÜCKTES FERROCEN

K.Schlögl und H.Seiler

Organisch-chemisches Institut der Universität Wien

(Received 24 February 1960)

VON überbrückten(bridged)Ferrocenen waren bisher nur solche Vertreter bekannt,in denen die (heteroannulare) Verknüpfung der beiden Cyclopentadienringe durch eine C-Kette erfolgt. Solche Verbindungen konnten durch intramolekulare Acylierung (Brücke von 3 C-Atomen)[1],über α,ω-Bis-cyclopentadienylalkane(Brücke: 3-5 C-Atome)[2] oder durch Acyloinringschluss von Ferrocen-1,1'-bisfettsäureestern (Brücke: 4-10 C-Atome)[3] erhalten werden.

Ausgehend vom ß-Ferrocenyl-propionsäuremethylester(I) (aus der entsprechenden Säure[4] mit Diazomethan erhalten),von der Ferrocen-1,1'-bispropionsäure(V)[3] oder auch vom einfach überbrückten Ferrocen(VIII)[2,3] gelang nun die Darstellung der zweifach überbrückten Verbindung : Bis-(trimethylen)-ferrocen(XIII).Von allen drei Ausgangsprodukten gelangt man dabei zur gleichen Schlüsselsubstanz ,dem überbrückten Keton(XII).

---

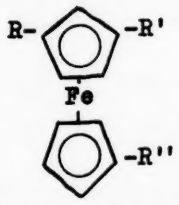
1 K.L.Rinehart,Jr.und R.J.Curby,Jr.,J.Amer.Chem.Soc.79, 3290 (1957).

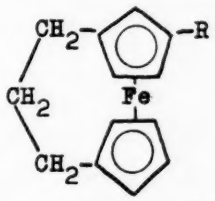
2 A.Lüttringhaus und W.Kullick, Angew.Chem. 70,438(1958).

3 K.Schlögl und H.Seiler, Mh.Chem. 91,79(1960).

4 K.Schlögl, Mh.Chem. 88,601 (1957).

1960





I R=H , R'= $(CH_2)_2COOMe$, R'' =H

II R=CHO , R'= $(CH_2)_2COOMe$, R'' =H

III R= CH=CHCOOH , R'=$(CH_2)_2COOH$, R''=H

IV R=R'= $(CH_2)_2COOH$, R'' =H

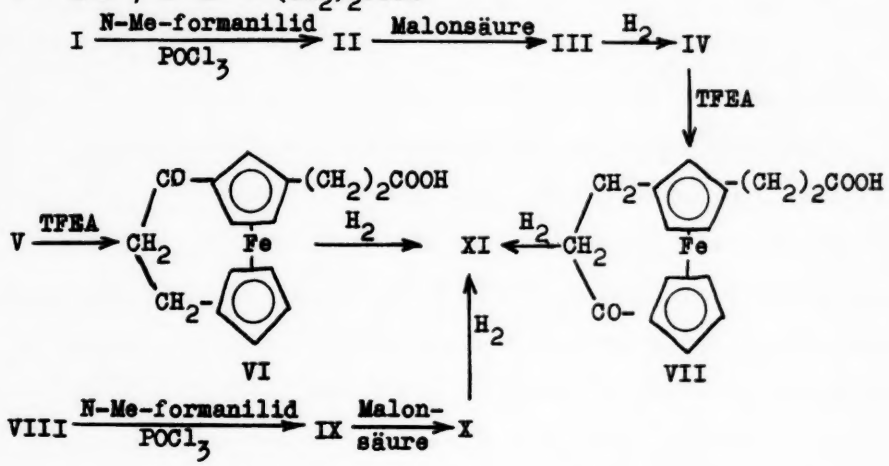
V R=H , R'=R'' = $(CH_2)_2COOH$

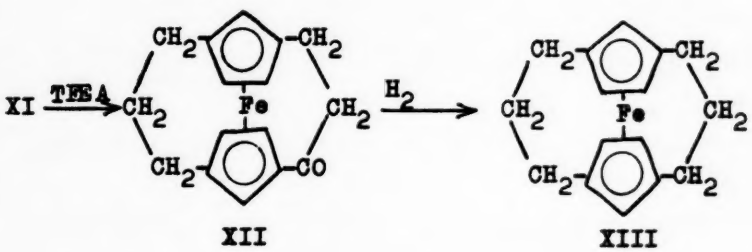
VIII R=H

IX R=CHO

X R= CH=CHCOOH

XI R= $(CH_2)_2COOH$





Zur Synthese wurden die folgenden vier Reaktionen herangezogen,die sich schon früher bei der Darstellung von Ferrocenderivaten bewährt hatten:

(1)Formylierung mit N-Methyl-formanilid und $POCl_3$ analog der Darstellung von Ferrocen-aldehyd[5].

(2)Knövenagel-Kondensation der Aldehyde(II,IX)mit Malonsäure und Hydrierung der Acrylsäuren (III,X) zu den entsprechenden Propionsäuren (IV,XI)[4,5].

(3)Ringschluss der Propionsäuren zu den Ringketonen (VI,VII ,XII)mit Trifluoressigsäure-anhydrid(TFEA)[7].

(4)Katalytische Hydrierung der Ringketone (in Eisessig mit PtO_2/H_2) zu den 1,1'-Trimethylen-verbindungen(XI,XIII).

Die Formylierung (mono)-substituierter Ferrocene scheint - wahrscheinlich wegen der Aktivierung des substituierten Ringes - zu homoannularer Substitution zu führen;die entsprechenden Produkte (II,IV)zeigen nämlich ebenso wie das aus Äthylferrocen gewonnene Formyl-äthyl-ferrocen und der daraus durch Reduktion erhältliche Alkohol (Äthyl-hydroxymethyl-ferrocen) im IR eine für einen unsubstituierten Cyclopentadienring charakteristische scharfe Bande bei 1105 cm^{-1} und daneben eine deutlich schwächere um 1000 cm^{-1} (9,10 μ-Regel[6]).

---

[5] G.D.Broadhead , J.M.Osgerby und P.L.Pauson , J.Chem. Soc. 650 (1958).

[6] M.Rosenblum , Chem.& Ind. 953 (1958) ; J.Amer.Chem. Soc. 81,4530 (1959) ; M.Rosenblum und R.B.Woodward, J.Amer.Chem.Soc. 80,5443 (1958) .

Die Annahme einer homoannularen Substitution wird ferner dadurch gestützt, daß die Bis-propionsäure (IV) mit der auf eindeutigem Weg erhaltenen 1,1'-Bis-verbindung(V)[3] nicht identisch ist.

Über die reaktionsfähigen Formylverbindungen dürfte sich somit ein bequemer Weg zur Darstellung homoannular(di-)substituierter Ferrocenderivate eröffnen.

Der Ringschluss von IV und V mit TFEA führte nur zur Monoacylierung (VI,VII), was auf Grund der Inaktivierung des Ferrocenmoleküls durch eine CO-Gruppe gegenüber einer zweiten Acylierung verständlich ist. Nach Hydrierung zur Ringpropionsäure(XI) jedoch, die auch aus VIII über IX und X erhältlich ist, liess sich glatt der zweite Ringschluss zum Keton(XII) erreichen, das nach neuerlicher Hydrierung das gewünschte Bis-(trimethylen)-ferrocen (XIII) lieferte.

Bis auf diese beiden letzten Verbindungen wurden von den Zwischenprodukten die Säuren nur papierchromatographisch[3] auf ihre Reinheit geprüft und die Aldehyde nach Chromatographie an Al_2O_3 IR-spektroskopisch charakterisiert.

Das 1,1'-Trimethylen-3,3'-(α-ketotrimethylen)-ferrocen (XII) schmolz nach chromatographischer Reinigung(Al_2O_3) und Umkristallisieren aus Methanol-Wasser von 110-113°. (Ber. für $C_{16}H_{16}FeO$: C, 68.60; H, 5.76; Gef.: C, 68.15; H, 5.83). 1,1'-Trimethylen-3,3'-trimethylen-ferrocen(XIII) wurde durch Chromatographie(Al_2O_3), Destillation (bei 0,3mm und 80-100° Luftbadtemp.) und Kristallisation (Methanol-Wasser) gereinigt.

Schmp. 88-91°.(Ber.für $C_{16}H_{18}Fe$: C, 72.20; H, 6.82; Gef.: C, 72.48; H, 6.89).

Die Frage nach der Stellung der beiden Brücken zueinander (1,2 oder α- bzw. 1,3 oder β-) kann auf Grund bereits vorliegender experimenteller und IR-spektroskopischer Befunde mit einiger Sicherheit zugunsten der 1,3-Substitution entschieden werden.Vor allem aus sterischen Gründen überwiegen bei Acylierungen von Alkylferrocenen die 1,3-disubstituierten Produkte.[6,7] Diese unterscheiden sich als solche ebenso wie nach Reduktion zu den Dialkylderivaten durch IR-Banden im Gebiet von 900 - 1000 cm^{-1} charakteristisch von den 1,2 -Isomeren.[6,7] Tatsächlich stehen ein beim Ringketon(XII) auftretendes Dublett (905 und 930 cm^{-1}) bzw. zwei sehr scharfe Banden (911 und 936 cm^{-1})beim Bis-trimethylen-ferrocen(XIII) in gutem Einklang mit Befunden bei Alkyl-acetyl- und Bis-alkylferrocenen ,bei denen die Stellung der Substituenten in 1,3 gesichert ist[6,7].

Die Aufnahme der IR-Spektren verdanken wir Herrn Dr.J.Derkosch.Für die Überlassung von Ferrocen haben wir Herrn Dr.V.Weinmayr,E.I.duPont de Nemours & Co,Wilmington(Del.) bestens zu danken.

---

[7] K.L.Rinehart,Jr., K.L.Motz und S.Moon , J.Amer.Chem. Soc. 79, 2749 (1957).

Tetrahedron Letters No. 7, 9-11, 1960. Pergamon Press Ltd. Printed in Great Britain.

CONSTITUTION OF VALERANONE

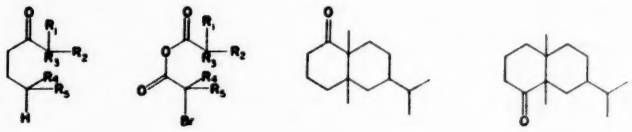
J. Křepinský, M. Romaňuk, V. Herout and F. Šorm

Institute of Organic Chemistry and Biochemistry,

Czechoslovak Academy of Science, Prague

(Received 21 February 1960)

RECENTLY, we determined partial structure (I) for valeranone, the bicyclic, saturated sesquiterpenic ketone $C_{15}H_{26}O$ from Valeriana officinalis L.,



I II IIIa IIIb

and proved its identity with jatamansone, isolated from Nardostachys jatamansi.[1] In the course of our further work we succeeded to elucidate the constitution of valeranone (IIIa or IIIb) by means of following reactions.

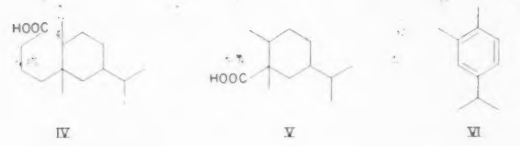
The natural ketone was submitted to photolysis in U.V.-light[2,3] to

[1] J. Křepinský, V. Herout and F. Šorm, Tetrahedron Letters No.3, 9 (1960).

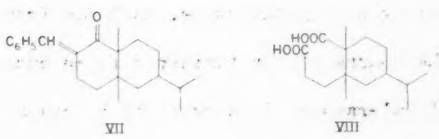
[2] G. Ciamician and P. Silber, Ber. 40, 2415 (1907).

[3] D. Arigoni, D.H.R. Barton, R. Bernasconi, C. Djerassi, J.S. Mills and R. Wolff, Proc. Chem. Soc. 306 (1959).

afford a saturated monocyclic acid of molecular formula $C_{15}H_{28}O_2$ (IV) which by three fold Barbier - Wieland degradation was converted into a monocarboxylic acid $C_{12}H_{22}O_2$ (V); this constitutes the proof that R_5 in formula I is hydrogen atom. As the bromoanhydride $C_{14}H_{21}O_3Br$ (II) failed to be dehydrobrominated[4] we take carbon atom R_4 as a quaternary one. We therefore dehydrogenated the acid $C_{12}H_{22}O_2$ (V) in the presence of palladized charcoal (30%) at 290-305° for 3 hr and obtained a uniform monocyclic aromatic hydrocarbon of molecular formula $C_{11}H_{16}$ (VI) which in view of its physical constants (d_4^{20} 0.8647; n_D^{21} 1.4942) and its infra-red spectrum was identical with an authentic sample of 1,2-dimethyl-4-isopropylbenzene (VI). The gaseous products of dehydrogenation were analysed by gas chromatography according to Janak; only hydrogen was estimated.



IV V VI



VII VIII

[4] T.R. Govindachari, B.R. Pai, K.K. Purushothaman and S. Rajadurai, Tetrahedron Letters No. 15, 5 (1959).

Further we dehydrogenated the monocyclic dicarboxylic acid $C_{15}H_{26}O_4$ (VIII), prepared by ozonolysis of monobenzylidene valeranone[1,4] (VII), under the conditions used for the acid $C_{12}H_{22}O_2$ (V) and obtained, besides neutral, hitherto non-identified products and regenerated starting material, a single monocarboxylic volatile acid which, by means of paper chromatography, was identified as propionic acid (butanol - 2N ammonia solution, R_F 0.24). In view of these results we take formula (IIIa or IIIb) for valeranone as proved.

This work will be published in full detail in Collection of Czechoslovak Chemical Communications together with further proof of this unusual structure and its stereochemistry.

1960

TL 78+

Tetrahedron Letters No. 7, pp. 12-16, 1960. Pergamon Press Ltd. Printed in Great Britain.

BEMERKUNGEN ZU DER ARBEIT VON S. M. BLOOM: "AN ACID STABLE CYCLOHEXADIENON"[1]

H. Budzikiewicz

Organisch-chemisches Institut, Universität Wien

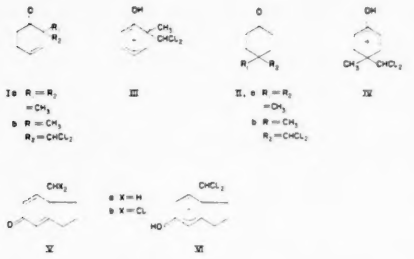
(Received 24 February 1960)

CYCLOHEXADIENONE vom Typus I und II lagern sich im allgemeinen unter dem Einfluss von Acetanhydrid/H^+, Acetanhydrid/BF_3, verdünnten Säuren oder BF_3-Ätherat in die entsprechenden Phenole um. R_1 und R_2 in I und II kann hiebei Alkyl,[2,3] Aryl,[4] OH oder $OCOCH_3$[5,6,7] usw. bedeuten. Für diese Umlagerungen wurde ein Mechanismus ausführlich diskutiert, der als ersten Schritt den Angriff einer Antibase (z.B. BF_3) oder eines Protons an den Carbonylsauerstoff annimmt.[5-9] S.M. Bloom ist es nun kürzlich gelungen,[1] diesen Mechanismus durch Auffinden eines säurestabilen Cyclohexadienons (Vb) zu stützen. Vb lässt sich nämlich in konz. Schwefelsäure unter Ausbildung eines "delokalisierten Ions"[1] (VI) auflösen und aus dieser Lösung durch

---

[1] S.M. Bloom, Tetrahedron Letters 21, 7 (1959).
[2] M. Yanagita, A. Tahara and E. Ohki, J.Pharm.Soc.Japan 71, 1060 (1951).
[3] E.N. Marvell and E. Magoon, J.Amer.Chem.Soc. 77, 2542 (1955).
[4] E.Schinzel and F. Wessely, Monatsh.Chem. 86, 912 (1955).
[5] F. Wessely and W. Metlesics, Monatsh.Chem. 85 637 (1954).
[6] S. Goodwin and B. Witkop, J.Amer.Chem.Soc. 79, 179 (1957).
[7] W. Metlesics, F. Wessely and H. Budzikiewicz, Tetrahedron 6, 345 (1959).
[8] S.M. Bloom, J.Amer.Chem.Soc. 80, 6280 (1958).
[9] H.Christol, R.Jacquier and M.Mousseron, Bull.Soc.Chim.Fr. 11 (1959).

Verdünnen mit Wasser wieder rückgewinnen.



Bloom[1] erklärt die Säurestabilität von Vb folgendermassen: Untersuchungen von Va haben ergeben[10], dass eine Umlagerung durch Änderung der Anellierung des Fünferringes (zum Unterschied von grösseren Ringsystemen[8,11,12]) nicht eintritt; es wandert vielmehr die anguläre Methylgruppe. Substituiert man nun diese so, dass die Bindung zum Kern schwerer zu lösen ist als bei einer CH_3-Gruppe, dann kann keine Umlagerung eintreten. Dies ist bei Vb der Fall. Das heisst mit anderen Worten, Vb ist gegen Säuren stabil, weil der Fünferring wegen zu grosser Spannungen im transition state und die $CHCl_2$-Gruppe wegen der zu festen C-C-Bindung nicht wandern kann.

Nach der Erklärung von Bloom müsste dann ein Cyclohexadienon, das am selben C-Atom eine $CHCl_2$-Gruppe und einen wanderungsfähigen Rest, z.B. CH_3- trägt, sich unter Säure-Katalyse umlagern lassen. Dies ist aber nicht der Fall:

IIa lässt sich in Acetanhydrid unter Zusatz katalytischer Mengen

---

10 S.M. Bloom, J.Amer.Chem.Soc. 81, 4728 (1959).

11 R.B. Woodward and T. Singh, J.Amer.Chem.Soc. 72, 494 (1950).

12 C.Djerassi and T.T.Grossnickle, J.Amer.Chem.Soc. 76, 1741 (1954).

Schwefelsäure in 3,4-Dimethylphenol umlagern.[2] IIb kann man jedoch ebenso wie Vb in konzentrierter Schwefelsäure auflösen und aus dieser Lösung durch Verdünnen mit Wasser in praktisch quantitativer Ausbeute wieder regenerieren. Das UV-Spektrum der schwefelsauren Lösung von IIb zeigt gegenüber einer äthanolischen Lösung von IIb eine ähnliche Verschiebung der Maxima wie Vb, die für die Ausbildung eines "delokalisierten Ions"[1] spricht. Dass IIb auch gegen verdünnte Säuren stabil ist, geht schon aus der Darstellungsmethode hervor, bei der das mit Schwefelsäure angesäuerte Reaktionsgemisch einer Wasserdampfdestillation unterworfen wird.[13]

In gleicher Weise lässt sich Ia[3,14] in Acetanhydrid unter Zusatz katalytischer Mengen Schwefelsäure bei Zimmertemperatur glatt zu 2,3-Dimethylphenol umlagern.[3] Bei Ib ist dies unter Einwirkung von Acetanhydrid und Schwefelsäure, Perchlorsäure oder Bortrifluorid-Ätherat trotz längerer Versuchsdauer und höherer Temperatur (50°) jedoch nicht gelungen. Es liess sich vielmehr auch hier immer nur unverändertes Ausgangsmaterial in guter Ausbeute zurückgewinnen. Das UV-Spektrum von Ib in konzentrierter Schwefelsäure zeigt ebenfalls eine Verschiebung der Maxima gegenüber einer Aufnahme in Äthanol.[15] Es liegt also auch hier ein VI entsprechendes "delokalisiertes Ion" vor (III). Aus der schwefelsauren Lösung lässt sich das Ausgangsdienon wieder durch Verdünnen mit Wasser regenerieren. Die Stabilitat von Ib gegen verdünnte Säuren beweist auch hier die Darstellungsweise, die analog IIb erfolgt.[16]

---

[13] K.v. Auwers and G. Keil, Ber.Dtsch.Chem.Ges. 35, 4207 (1902).
[14] K. Alder, F.H. Flock and H. Lessenich, Chem.Ber. 90, 1709 (1957).
[15] J. Derkosch and W. Kaltenegger, Monatsh.Chem. 88, 778 (1957).
[16] K.v. Auwers and M. Hessenland, Ber.Dtsch.Chem.Ges. 41, 1805 (1908).

1960

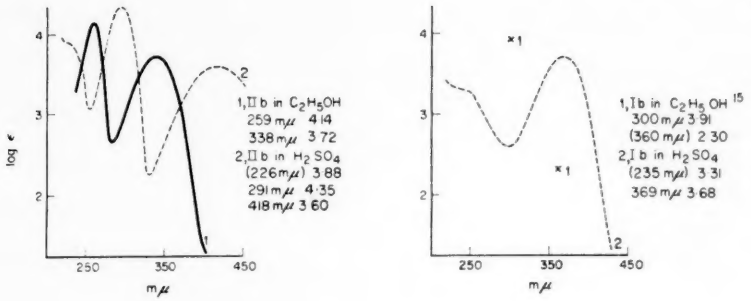
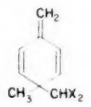


FIG. 1.

Aus diesem Ergebnis wäre zu folgern, dass die $CHCl_2$-Gruppe imstande ist, die 1,2-Wanderung der Methylgruppe und vielleicht auch die anderer Gruppen zu verhindern und so die Umlagerung hintanzuhalten. Es dürfte also eine allgemeine Eigenschaft derartiger Verbindungen sein, dass sie der säurekatlysierten Dienon-Phenol-Umlagerung nicht unterliegen.



VII, a. X = H
b. X = Cl

TL 7C

Dies würde auch das Ergebnis von K. v. Auwers[17] erklären, dass VIIa sich unter Einwirkung verdünnter Säuren leicht umlagert, VIIb hingegen unter diesen Bedingungen stabil ist. VIIb lässt sich erst durch heisse konzentrierte Schwefelsäure und nachfolgende Wasserdampfdestillation in 2,4-Dimethylbenz-

---

[17] K. v. Auwers and K. Ziegler, Ann.Chem. 425, 243 (1921).

aldehyd überführen,[18] eine Reaktion, die dadurch zu erklären wäre, dass die $CHCl_2$-Gruppe primär zu einer CHO-Gruppe verseift wird und dann, nach Wegfall der "sperrenden" $CHCl_2$-Gruppe, eine normale Dienon-Phenol-Umlagerung unter Methylwanderung erfolgt.

Dem Vorstand des Institutes, Herrn Prof. Dr. F. Wessely, möchte ich an dieser Stelle dafür danken, dass er mir die Durchführung dieser Arbeit ermöglichte.-

---

[18] K.v. Auwers and M. Hessenland, Ann.Chem. 352, 284 (1906).

Tetrahedron Letters No. 7, pp. 17-23, 1960. Pergamon Press Ltd. Printed in Great Britain.

DIBORANE REDUCTION OF CARBOXYL GROUPS IN CARBOHYDRATES

F. Smith and A. M. Stephen

Department of Agricultural Biochemistry,

University of Minnesota, St. Paul 1, Minnesota

(Received 8 February 1960; in revised form 3 March 1960)

ESTER and lactone groups in carbohydrate compounds may be reduced by complex metal hydrides in aqueous solution[1,2] or in dry ether-type solvents.[3,4,5] Reduction of carboxyl groups may also be effected by lithium aluminum hydride[6] and related metal hydrides, but the method is limited to carboxylic acids soluble in organic solvents which are not affected by the reducing agent.[7] Consequently it has been possible to convert a methylated acidic polysaccharide into a methylated neutral polysaccharide[4] by carrying out the reduction in tetrahydrofuran but our attempts to reduce an acylated acidic polysaccharide have failed because the ester groups are attacked first and as a result acidic polysaccharide

---

[1] M. L. Wolfrom and H. B. Wood, J. Amer. Chem. Soc. 73, 2933 (1951).

[2] M. L. Wolfrom and K. Anno, J. Amer. Chem. Soc. 74, 5583 (1952).

[3] B. Lythgoe and S. Trippett, J. Chem. Soc. 1983 (1950).

[4] M. Abdel-Akher and F. Smith, Nature, London 166, 1037 (1950).

[5] F. Smith and R. Montgomery, Chemistry of Plant Gums and Mucilages, pp. 140-144. Reinhold Corp., New York (1959).

[6] R. F. Nystrom and W. G. Brown, J. Amer. Chem. Soc. 69, 2548 (1947).

[7] N. G. Gaylord, Reduction with Complex Metal Hydrides. Interscience, New York and London (1956).

material is precipitated from the reaction mixture.[8] Since diborane has been shown to reduce carboxyl groups in preference to ester groups[9] it seemed likely that this reducing agent might well be capable of reducing carboxyl groups in suitable derivatives of both simple and complex carbohydrate compounds.

We wish to report herein the successful transformation of the -COOH group to $-CH_2OH$ not only in monosaccharide acids but also in acidic polysaccharides. Our preliminary experiments indicate that diborane reduction of acidic carbohydrates is a general reaction and that the production of neutral polysaccharides from acid polysaccharides such as pectic substances, acidic hemicelluloses, plant gums and mucilages is within the scope of the reaction. The new method also opens up the possibility of producing certain sugars and their derivatives (e.g. L-gulose from alginic acid and 4-O-methyl-D-glucose from mesquite gum) by a more direct route than has hitherto been available. It is also apparent that the effect of uronic acid residues on the physical, chemical and immunological properties of polysaccharides can now be investigated.

The reductions were conducted in bis (2-methoxyethyl) ether ("diglyme")[10] solution at room temperature. Diborane was generated[11] in situ by slowly adding boron trifluoride etherate in ether-diglyme to the product obtained by mixing solutions in diglyme of the carbohydrate

---

[8] F. Smith and D. Spriestersbach, unpublished.

[9] H. C. Brown and B. C. Subba Rao, J. Org. Chem. 22, 1135 (1957).

[10] H. C. Brown, E. J. Mead and B. C. Subba Rao, J. Amer. Chem. Soc. 77, 6209 (1955).

[11] H. I. Schlesinger, H. C. Brown, H. R. Hoekstra and L. R. Rapp, J. Amer. Chem. Soc. 75, 199 (1953); H. C. Brown and P. A. Tierney, Ibid. 80, 1552 (1958).

acid and of sodium borohydride.[9] Sodium borohydride and boron trifluoride were employed throughout in the molar ratio 3:4, but the quantity of reducing agent used per carboxyl group was varied.

(1) Reduction of methyl α-D-galactopyranosiduronic acid to methyl α-D-galactopyranoside. Methyl α-D-galactopyranosiduronic acid, prepared by saponifying the corresponding methyl ester (0.9 millimoles), was reduced during 3 hr. by sodium borohydride (2.6 millimoles) and boron trifluoride etherate (3.5 millimoles) in diglyme solution. The product was kept overnight, diluted with ice-water, deionized with exchange resins, and concentrated: measurement of $[\alpha]_D$ of the syrupy residue indicated 48% conversion, based upon the ester glycoside, to methyl α-D-galactopyranoside. The crystalline hydrate, m.p. 106° (undepressed by an authentic specimen), $[\alpha]_D^{21}$ + 180° (c 0.7), was obtained from a portion of the product; the remainder was hydrolyzed with acid in the usual way to give chromatographically pure D-galactose, characterized as its p-nitroaniline derivative, m.p. and mixed m.p. 215-216°.

(2) Reduction of methyl 2,3,4-tri-O-methyl-α-D-galactosiduronic acid to methyl 2,3,4-tri-O-methyl-α-D-galactoside. Methyl 2,3,4-tri-O-methyl α-D-galactopyranosiduronic acid, prepared as in (1) by saponification of its methyl ester, was reduced under the same conditions. The product, after terminating the reaction by addition of ice-water, was isolated by chloroform extraction and hydrolysed with acid to give 2,3,4-tri-O-methyl-D-galactose, $[\alpha]_D^{20}$ + 93° (c 5.6), in 56% overall yield. The sugar, which was chromatographically pure, was characterized by conversion to the aniline derivative, m.p. and mixed m.p. 168-169° after recrystallization from ethanol.

In an experiment carried out under the same conditions except that

no boron trifluoride was added, no detectable reduction of the acid occurred.

(3) Conversion of galactaric acid to galactitol. Tetra-O-acetyl-galactaric acid, dried thoroughly at 130° in vacuo, was reduced by the same general technique, using twice the amount of reducing agent for each carboxyl group as was employed in (1) above. The reaction mixture was then neutralized (aqueous sodium carbonate) and evaporated in vacuo to near dryness. The residue containing partially acetylated galactitol was boiled under reflux with acetic anhydride to dissociate any borate complex and to ensure complete acetylation.[12,13] Most of the residual acetic anhydride and diglyme was distilled in vacuo and the reaction mixture was poured into ice-water with stirring. The hexa-O-acetyl-galactitol, recovered in 75% yield by extraction with chloroform and evaporation of solvent, had m.p. 169-171° (after recrystallization from ethanol).

(4) Reduction of mesquitic acid acetate. Similar proportions of the reducing combination to those employed in the first two experiments were used in the reduction of the acetyl derivative,[14] $[\alpha]_D^{26}$ + 68° (c 1.2, $CHCl_3$), of mesquitic acid from mesquite (Prosopis juliflora D.C.) gum, the product being recovered by neutralization with ice-cold alkali followed by chloroform extraction. The partially-acetylated polymer, $[\alpha]_D^{25}$ + 70° (c 2.6, $CHCl_3$), obtained from the dried chloroform extract, gave (paper chromatography) upon hydrolysis with dilute acid

---

12 M. Abdel-Akher, J. K. Hamilton and F. Smith, J. Amer. Chem. Soc. 73, 4691 (1951).

13 H. Klosterman and F. Smith, J. Amer. Chem. Soc. 74, 5336 (1952).

14 J. F. Carson and W. D. Maclay, J. Amer. Chem. Soc. 68, 1015 (1946).

arabinose, galactose, 4-O-methylglucose (from reduced 4-O-methyl-D-glucuronic acid residues) and a small proportion of 4-O-methyl-D-glucuronic acid.

In order to improve the conversion of acid to neutral groupings, a second experiment was conducted using five times the relative quantity of reducing agents. Worked up as before, the polysaccharide (partly de-acetylated) appeared in the aqueous layer, which was evaporated to dryness *in vacuo*. The residue was warmed with 0.1 N-sodium hydroxide to complete the de-acetylation process, and the polysaccharide was purified by repeated precipitation from aqueous solution with ethanol-ether mixtures, by dialysis, and by treatment with ion-exchange resins. Reduced mesquitic acid, $[\alpha]_D^{20}$ + 70° (*c* 1.36, aqueous alkali), equiv., 10,000 (approx.) (by titration with 0.02 N-sodium hydroxide using phenolphthalein as indicator), was recovered in excellent yield. The equiv. represents a reduction of nearly 90% of the original carboxyl groups to primary alcohol. Acid hydrolysis of a small portion of the product gave a mixture of the sugars arabinose, galactose, and 4-O-methylglucose. Only traces of uronic acid, together with unidentified reducing substances which may be artefacts, were detectable by paper chromatography.

On graded hydrolysis with 0.01 N-sulfuric acid at 100° for 14 hr. the reduced mesquitic acid yielded 30% of its weight of arabinose but little or no other reducing sugar was generated. The residue was fully hydrolyzed by heating at 95° for 8 hr. with N-sulfuric acid. From the neutralized (barium carbonate) hydrolysate, 4-O-methyl-D-glucose, $[\alpha]_D^{20}$ + 69° (*c* 1.45, MeOH), was separated by cellulose column chromatography and characterized as its phenylosazone, m.p. and mixed m.p. 158-159°,

$[\alpha]_D^{21}$ - 22° → 0° (equil.) (c 0.9, EtOH). The 4-O-methyl-D-glucose constituted 8% of the weight of reduced mesquitic acid hydrolysate. Assuming that the equiv. of mesquitic acid is 1300, this yield represents a recovery of 4-O-methyl-D-glucose of approx. 60%.

(5) Reduction of pectic acid acetate.[15] The acetylated derivative of pectic acid (prepared from citrus pectin), when reduced under the conditions used in the first mesquitic acid experiment and re-acetylated, yielded a chloroform-soluble acetylated galactose polymer which on acid hydrolysis gave galactose and only traces of galacturonic acid (paper chromatographic analysis).

(6) Reduction of alginic acid propionate. Since alginic acid[16] acetate was not sufficiently soluble in diglyme, a dipropionate, $[\alpha]_D^{20}$ -150° (c 1.0, pyridine), was prepared,[14] and reduced under the conditions used in the second mesquitic acid experiment. The reaction mixture was dialyzed and concentrated, and after saponification and several precipitations from aqueous solution with ethanol-ether, a polysaccharide was recovered which had equiv., 1000 and $[\alpha]_D^{20}$ - 86° (c 0.8, aqueous alkali). The equiv. represents 82% conversion of carboxyl groups to primary alcohol. Paper chromatographic and ionophoretic examination of the acid hydrolysate showed the presence of mannose, with smaller amounts of gulose.[17] Unreduced mannuronic acid was also detected as well as traces of glucose and pentoses, possibly arabinose and xylose.

---

15 Cf. G. O. Aspinall and A. Cañas-Rodriguez, J. Chem. Soc. 4020 (1958).

16 Kindly supplied by Kelco Company, San Diego, California, courtesy Dr. A. Miller.

17 F. G. Fischer and H. Dörfel, Z. physiol. Chem. 302, 186 (1955).

Acknowledgements. One of us (A.M.S.), on leave of absence from the University of Cape Town, South Africa, holds an appointment supported by the International Cooperation Administration under the Visiting Research Scientists Program administered by the National Academy of Sciences of the United States of America.

The authors are indebted to Dr. G. Zweifel, Purdue University, for preliminary discussion of the possibilities of the method and to the National Science Foundation for support.

1960

Tetrahedron Letters No. 7, pp. 24-26, 1960. Pergamon Press Ltd. Printed in Great Britain.

AN X-RAY STUDY OF THE CONFIGURATION OF CEVINE

W. T. Eeles

Viriamu Jones Laboratory, University College, Cardiff

(Received 7 March 1960)

THE structure and configuration of cevine have been the subject of extensive study. Milestones in their elucidation were the deduction of the form of the skeleton,[1] and the assignment of the hydroxyl groups.[2] Recently

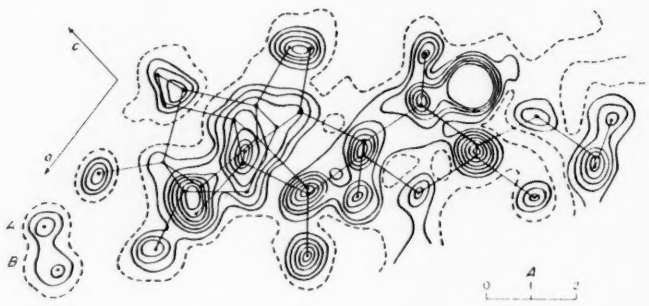


FIG.1. Electron-density map of cevine hydroiodide [010] projection, space group $P2_1$, $\underline{a}$ = 7.7, $\underline{b}$ = 10.8, $\underline{c}$ = 17.4A, β = 97°. Two molecules per unit cell.

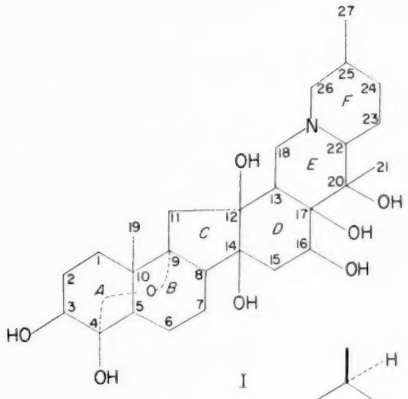
---

[1] W.A. Jacobs and S.W. Pelletier, J. Org. Chem. 18, 765 (1953).

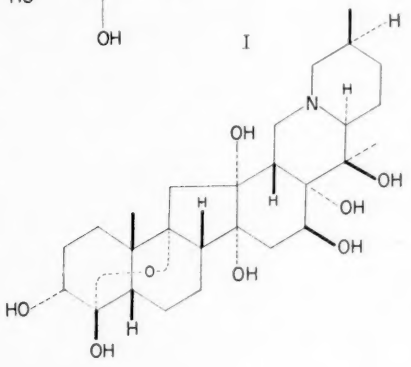
[2] D.H.R. Barton, O. Jeger, V. Prelog and R.B. Woodward, Experientia 10, 81 (1954).

comprehensive evidence of the relative configuration of the various centres of asymmetry has been published.[3]

The author has been engaged in the study of various cevine derivatives by X-ray crystallographic methods, and has independently arrived at the configuration given in ref. 3. The evidence for this is presented in Fig.1 which shows a projected electron-density map of cevine hydroiodide. Hydrogen atoms are beyond the limits of resolution but the other constituents show up clearly. In addition to the cevine molecule and its associated iodine atom



I



II

[3] S.M. Kupchan, W.S. Johnson and S. Rajagopalan, Tetrahedron 7, 47 (1959).

there are two molecules of water of crystallization, A and B. Though some of the carbon and oxygen atoms are not individually resolved, their positions can be inferred with the aid of plausible wire models of the cevine molecule. The models which were used were based on the formula I (formula XXXI of ref. 2), and the only one which satisfies the X-ray data has the configuration II. This is identical with that given in ref. 3.

With the exception of the configuration at C_{20} the X-ray data constitutes conclusive evidence of all the stereochemical features of cevine. Little need be said here about the A-B-C system except that the hydroxyl at C_3 is equatorial and all three rings are somewhat distorted, C being non-planar. The rings E,D and F are a system of trans-fused 'chairs' with C_{27} and the hydroxyls at C_{12},C_{14},C_{16} and C_{17} in axial dispositions. The arrangement of the methyl and hydroxyl groups at C_{20} which is favoured is that shown in II; but the distinction between the two possibilities rests on the actual heights of peaks and these are not sufficiently accurate to preclude the alternative arrangement.

This investigation is continuing and it is hoped that full crystallographic details will be publishable elsewhere in the near future. The author wishes to acknowledge his indebtedness to Professor A.J.C. Wilson and his staff for advice and help with the computations, and to Professor D.H.R. Barton for providing specimens.

Tetrahedron Letters No. 7, pp. 27-29, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

THE REACTION OF DICHLOROCARBENE WITH ANTHRACENE

R. W. Murray

Bell Telephone Laboratories, Incorporated

Murray Hill, New Jersey, U.S.A.

(Received 9 March 1960)

THE reaction of dichlorocarbene with olefins has been demonstrated to provide a convenient route to cyclopropanes.[1] Although it has been demonstrated[2] that the Reimer - Tiemann reaction involves a dichlorocarbene intermediate, there have been no reports of dichlorocarbene reacting with unsubstituted aromatic hydrocarbons.

Chromatography on alumina of the crude product of the reaction of chloroform with a benzene slurry of anthracene and potassium t-butylate afforded a white crystalline compound, (I), (10%), m.p. 128 - 129°. Found: C, 76.0; H, 6.39; Cl, 11.8. Calc. for $C_{19}H_{19}ClO$: C, 76.4; H, 6.41; Cl, 11.9. The ultraviolet spectrum of I (λ_{max}^{EtOH} 282 mμ, log ε = 4.04) is in good agreement with that of dibenzo [a,e]- cycloheptatriene.[3]

---

[1] W. von E. Doering and A.K. Hoffman, J. Amer. Chem. Soc. 76, 6162 (1954); W. von E. Doering and W.A. Henderson, Jr., Ibid. 80, 5274 (1958); W.E. Parham, H.E. Reiff and P. Swartzentruber, Ibid. 78, 1437 (1956); S.M. McElvain and P.L. Weyna, Ibid. 81, 2579 (1959).

[2] J. Hine and J.M. van der Veen, J. Amer. Chem. Soc. 81, 6446 (1959).

[3] T.W. Campbell, R. Ginsig and H. Schmid, Helv. Chim. Acta 36, 1489 (1953).

The absence of benzylic chlorine in I was demonstrated by its failure to react with alcoholic silver nitrate. The nuclear magnetic resonance spectrum (CCl_4) of I has aromatic peaks at 2.27 and 2.79, a methine peak at 5.08, and a methyl peak at 8.73.[4] The peak area ratios are approximately 9:1:9 for aromatic methine: methyl protons.

When I dissolved in concentrated sulfuric acid, a deep red solution of the 10-chlorodibenzotropylium ion, IV, was obtained. The ultraviolet and visible spectrum of this solution is in agreement with those of the dibenzo [a,e]tropylium cation, V, and the 5-phenyldibenzo[a,e]tropylium cation, VI,[5] with some shifts due to the presence of the chlorine substituent (Table 1). On the basis of the evidence given, I can reasonably be formulated as 10-chloro-5-t-butoxydibenzo[a,e]cycloheptatriene.

TABLE 1

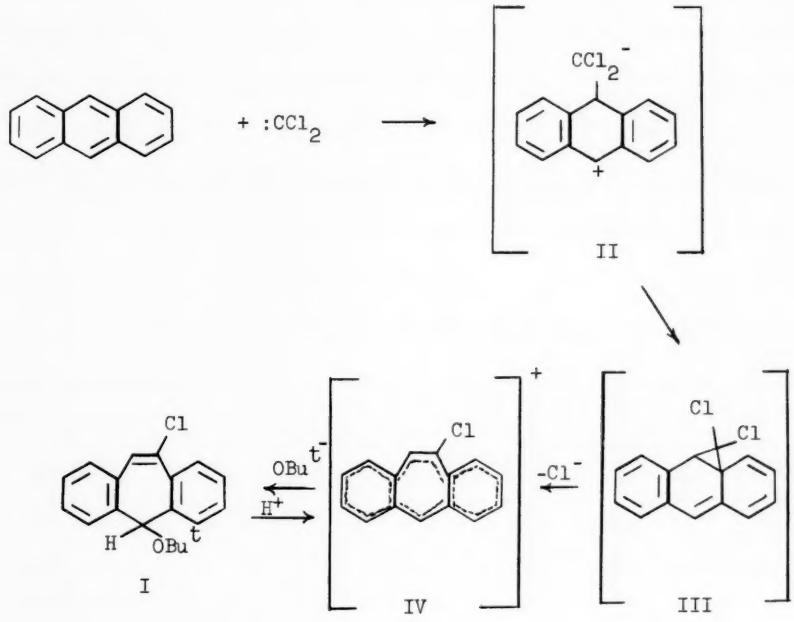
Absorption Maxima in 98% Sulfuric Acid

Ion	λ	log ε	λ	log ε	λ	log ε	λ	log ε	λ	log ε	λ	log ε	λ	log ε
IV	246	4.10	255	4.09	311	4.84	384	3.96	400	3.81	513	3.48	545	3.51
V	236	4.16	270	3.84	306	5.09	380	4.02	398	3.95	508	3.52	540	3.51
VI	240	4.26	268	4.10	312	5.01	384	3.76	414	3.70	528	3.65	564	3.69

[4] Chemical shift values are in p.p.m. relative to tetramethylsilane standard = 10.0 p.p.m. NMR spectra are by Dr. M. Saunders, Sterling Chemistry Laboratory, Yale University, New Haven, Connecticut.

[5] G. Berti, J. Org. Chem. 22, 230 (1957).

One possible mechanistic explanation for the formation of I involve the addition of dichlorocarbene to anthracene to give an intermediate zwitterion, II, which can close to the norcaradiene-type structure, III. This species would be expected to lose chloride ion to give the 10-chlorodibenzotropylium ion, IV, which in the presence of potassium t-butylate goes to the product, I.



The scope of this reaction with respect to other carbenes and other aromatic hydrocarbons is being investigated.

Tetrahedron Letters No. 7, pp. 30-32, 1960. Pergamon Press Ltd. Printed in Great Britain.

TURBICORYN, A NEW GLUCOSIDE OBTAINED FROM THE SEEDS OF A SACRED PLANT

M. C. Pérezamador and J. Herrán

Instituto de Quimíca, Universidad Nacional Autónoma de México

(Received 14 March 1960)

IT is well known that the Aztecs regarded several plants as sacred, examples being the hallucinatory mushrooms which have been thoroughly studied in recent years.

Another plant that seems to have been used was known as "Ololiuhqui." Although there has been some confusion in regard to the botanical identity of this plant, we were able to secure from the southern part of Mexico a sample of the seeds of Turbina corymbosa (Roth) Rasin (instead of Rivea corymbosa Hall), which is known in the place of origin by the trivial name already mentioned.[1]

From these seeds, after extraction with hexane to eliminate the oils, a new glucoside, which we propose to name Turbicoryn, was obtained from the alcoholic extract. The white crystals, obtained by purification and recrystallization from methanol-water, showed m.p. 240-241°; $[\alpha]_D^{25}$ -53°

[1] We wish to thank Mr. Thomas MacDougall for the botanical classification and the collection of the seeds.

(pyridine) (Found: C, 59.36; H, 8.44; O, 32.16. $C_{27}H_{46}O_{11}$ requires C, 59.32; H, 8.48; O, 32.19%).[2]

On acetylation of nona-acetate was obtained; m.p. 247-249°; $[\alpha]_D^{25}$ -59° (pyridine) (Found: C, 58.38; H, 7.10; O, 34.67; AcO, 41.04; M, (Rast) 1002. $C_{45}H_{64}O_{20}$ requires C, 58.43; H, 6.97; O, 34.59; 9 AcO, 41.8%, M, 925).

After hydrolysis of Turbicoryn with β-glucosidase, glucose, identified by paper chromatography, was obtained and a new aglycone Turbicorytin isolated; m.p. 151-153°; $[\alpha]_D^{25}$ -55° (pyridine) (Found: C, 65.45; H, 9.42; O, 25.15; CMe, 4.43; M, (Rast) 426. $C_{21}H_{36}O_6$ requires C, 65.59; H, 9.44; O, 24.97, CMe, 3.90%, M, 384.5).[3]

The aglycone, Turbicorytin, does not show unsaturation on test with tetranitromethane or bromine water, nor by titration with perbenzoic acid. It does not reduce Tollens reagent. On titration with periodic acid, two equivalents are found to be used, showing that the molecule contains at least three vicinal hydroxyl groups or is a bis-glycol. The product so obtained gives positive tests for aldehyde and can be oxidized to an acid or reduced with $LiAlH_4$ to an alcohol.

The acetylation of Turbicorytin with acetic anhydride-pyridine gives a hexa-acetate, m.p. 236-238°, showing that all six oxygens are in alcoholic functions; $[\alpha]_D^{25}$ -53° (pyridine) (Found: C, 62.19; H, 7.61; O, 30.40; AcO 41.8. $C_{33}H_{48}O_{12}$ requires C, 62.25; H, 7.60; O, 30.15; 6 AcO, 40.5%).

When Turbicorytin is heated with zinc dust at 400° under nitrogen, an oil is obtained and chromatography on alumina afforded a crystalline fraction,

---

[2] Micro-analysis carried out by F. Pascher, Bonn, Germany.

[3] Analysis carried out by Mr. J.M.L. Cameron, Glasgow, Scotland.

which sublimed at 60°/0.02 mm, m.p. 89-91°. In the ultra-violet it shows (in methanol) the maxima corresponding to a methyl-substituted phenanthrene, although the very small amount of this product available was not sufficient for purposes of complete characterization: λ_{max} 212 (4.42), 248 (4.47), 255 (4.58), 276 (3.96), 286 (3.94), 298 (4.04), 317 (2.48), 326 (2.38), 333 (2.53), 340 (2.28), 349.5 (2.40). The orange picrate has m.p. 132-134°.

Further work is being carried out to elucidate the complete structure of Turbicoryn and Turbicorytin and to determine whether they possess pharmacological activity.

Tetrahedron Letters No. 7, pp. 33-36, 1960. Pergamon Press Ltd. Printed in Great Britain.

INDOLE RING FORMATION FROM β,β-DIPHENYLETHYLENEAZOBENZENE

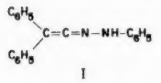
Harry H. Wasserman and Harry R. Nettleton

Contribution No. 1603, Department of Chemistry,

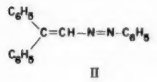
Yale University, New Haven, Connecticut

(Received 15 February 1960; in revised form 15 March 1960)

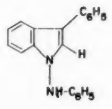
SOME years ago, Zerner and Goldhammer reported[1] that the red dehydration product (A) of diphenylglycolaldehyde phenylhydrazone, which they considered to be I, was a precursor of a new dimer of diphenylketene. In the course of reinvestigation of the reactions of A (in which we failed to



I



II



III

detect any diphenylketene dimer) we have found that A should be reformulated as II, and that in acid it undergoes isomerization to III. The change II ⟶ III represents an

[1] E. Zerner and H. Goldhammer, Monatsh. 54, 485 (1929).

unusual method of forming an indole derivative which, in a later step, can undergo reductive cleavage of the N-N linkage.

Compound A, m.p. 72°, (Anal. Calcd. for $C_{20}H_{16}N_2$: C, 84.48; H, 5.67; N, 9.85. Found: C, 84.37; H, 5.71; N, 10.12) was prepared according to the method of Zerner by the dehydration of diphenylglycolaldehyde phenylhydrazone[2] (IV) in dilute sulfuric acid. IV, prepared from the reaction of ethyl diazoacetate with excess phenylmagnesium bromide, was identical with the material, m.p. 130°, derivable from (a) the condensation of diphenylglycolaldehyde with phenylhydrazine, or (b) the addition of phenylmagnesium bromide to phenylglyoxal phenylhydrazone.

Structure I for A was ruled out on the following grounds: (i) Related ketenimines undergo rapid hydration to amides under the conditions leading to the formation of A.[3] (ii) The infrared spectrum of A lacks both the 3 μ (NH) and the 5 μ (>C=C=N-) absorption bands expected of I.[3] The conjugated (ethyleneazobenzene) structure (II), on the other hand, fits the spectroscopic as well as the chemical[4] evidence. In particular, there is close correspondence between the ultraviolet absorption spectrum of A and the spectrum of the related ethyleneazobenzene formed by air oxidation of

---

[2] E. Zerner, ibid. 34, 1609 (1913).

[3] C. L. Stevens and J. C. French, J. Am. Chem. Soc., 75, 657 (1953).

[4] Among other reactions, the reduction of A to diphenylacetaldehyde phenylhydrazone by zinc in ethanolic KOH.

9-formylfluorene phenylhydrazone.[5]

On warming a solution of II in acetic acid in the presence of a trace of sulfuric acid, a gradual conversion takes place to a colorless isomer, B, m.p. 140°, which shows NH absorption in the infrared (Anal. Found: C, 84.48; H, 5.46; N, 9.86; Mol. wt., 242). The key to the structure of B was provided by its ultraviolet absorption spectrum. As shown in Fig. 1, the spectrum of B is strikingly similar to the spectrum obtained by adding the molar extinction coefficients of aniline and 3-phenylindole. This suggests that B is N-anilino-3-phenylindole(III). In confirmation of this assignment, it was found that when B is heated in ethylene glycol, it undergoes cleavage to 3-phenylindole.

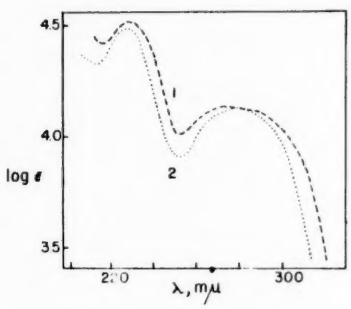
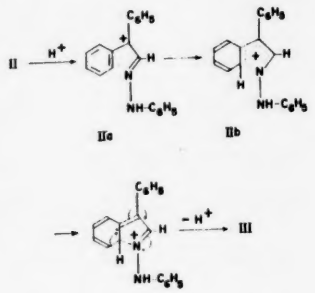


FIG. 1. Ultraviolet absorption spectra in ethanol Curve 1 (----), Compound B (III); Curve 2 (••••) obtained by adding the extinction coefficients of the aniline and 3-phenylindole spectra.

[5] W. Wislicenus and K. Russ, Ber. 43, 2719 (1910).

The conversion of II to III may be pictured as shown: Cyclization of the protonated species IIa takes place through the transition state IIb, and leads to the product, III.



1960

19

Tetrahedron Letters No. 8, pp. 1-10, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

ON THE CHEMICAL CONSTITUTION OF OBACUNONE

T. Kubota, T. Kamikawa T. Tokoroyama and T. Matsuura.

Faculty of Science, Osaka City University, Osaka, Japan

(Received 1 March 1960; in revised form 15 March 1960)

SINCE the isolation of obacunone $C_{26}H_{30}O_7$(I), a bitter principle of Rutaceae, from Phelledendron amurense, Rupr. by Murayma and Takata[1] in 1928, it has been investigated by many workers.[1-5] Kaku and Ri[2] showed that (I) possessed two lactones (one, α-β-unsaturated) and a keto group. Later Kubota and Tokoroyama[4] proved that one of the two remaining oxygens belonged to a furan ring and suggested that the other could be assigned to an ether linkage. In 1958, Dean and Geissman[5] proposed a partial structure (IA) for obacunone based on the results of spectral studies. In continuation of our earlier studies, we should now like to record some observations which lead to the assignment of another partial structure (IB) to this substance.

(i) The number of double bonds in abacunone (Scheme 1 and Fig. 1)

Ter 8/1

As a result of ozonization of obacunone hydrochloride (II) three carbons were lost giving ethioobacunoic acid hydrochloride (III) $C_{23}H_{29}O_8Cl$,

---

1 Y. Murayama and J. Takata, J.Pharm.Soc.Japan 47, 1037 (1928).

2 T. Kaku, C. Cho and T. Orita, J.Pharm.Soc.Japan 52, 594 (1932).

3 O.H. Emerson, J.Amer.Chem.Soc. 70, 545 (1948); 73, 2621 (1951); 74, 688 (1952).

4 T. Kubota and T. Tokoroyama, Chem. & Ind. 298 (1957).

5 F.M. Dean and T.A. Geissman, J.Org.Chem. 23, 596 (1958).

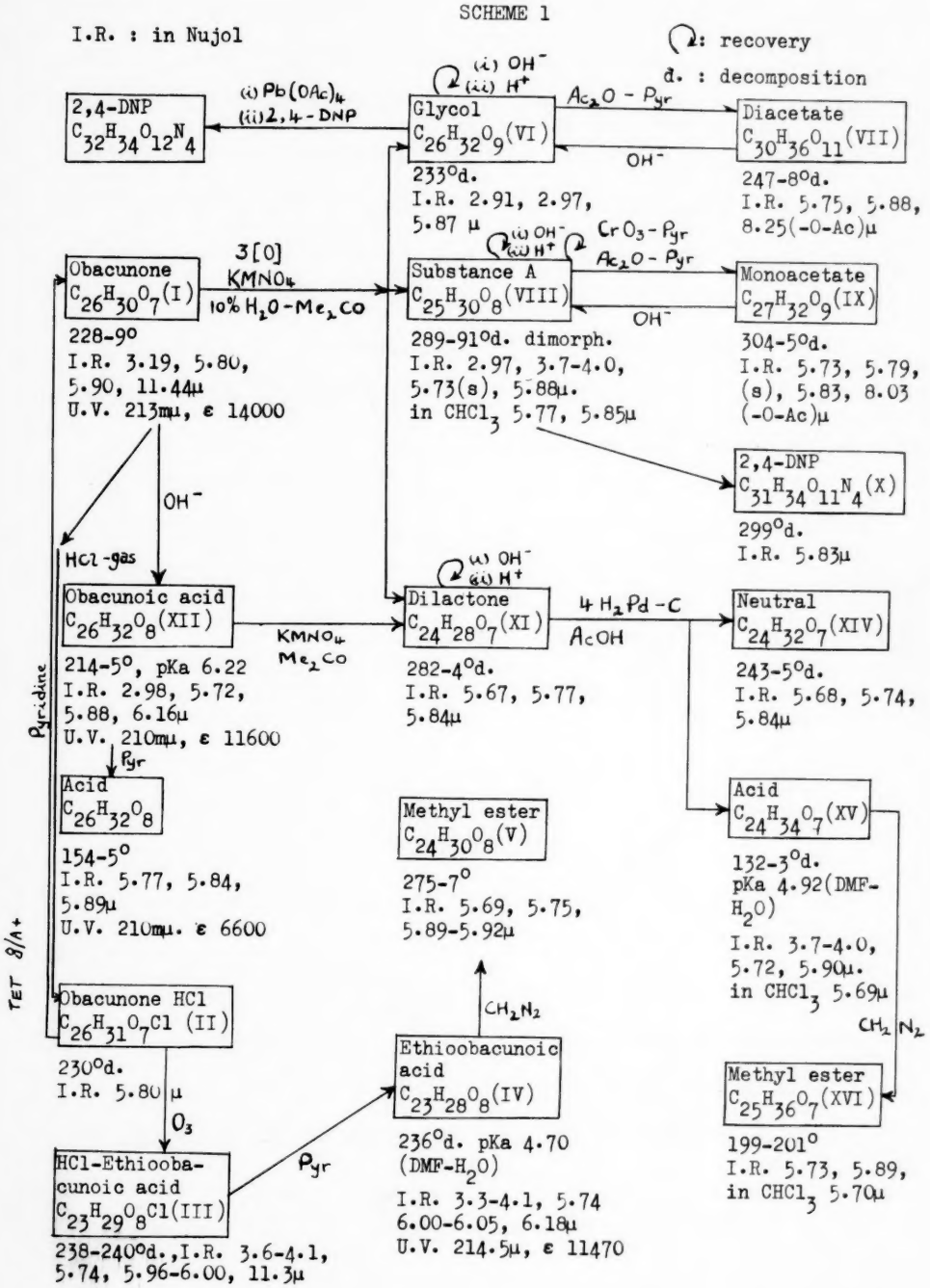
which, in turn, was dehydrochlorinated in pyridine to ethioobacunoic acid (IV), $C_{23}H_{28}O_8$. The spectral data of IV, [U.V. 214.5 mμ (ε 11,500), I.R. 6.18] indicated that the α,β-unsaturated lactone was regenerated and the furan ring destroyed on ozonization. Since the ester of III gave a negative test with tetranitromethane and has no appreciable absorption above 205 mμ, (ε_{210} 400), it must be a saturated substance. Obacunone (I), therefore, has no unsaturation other than the furan ring and the α,β-unsaturated lactone group.

(ii) <u>The α,β-unsaturated 7-membered lactone ring in obasunone (Scheme 1 and Fig. 1)</u>

The following three compounds were obtained when obacunone (I) was oxidized with potassium permanganate in acetone solution: (a) A glycol (VI), $C_{26}H_{32}O_9$ [diacetate (VII) $C_{30}H_{36}O_{11}$; lead tetraacetate value, 0.9; periodate value, 1.6], (b) A substance A (VIII), $C_{25}H_{30}O_8$ [monoacetate (IX), $C_{27}H_{32}O_9$; mono-2,4-dinitrophenylhydrozone (X), $C_{31}H_{34}O_{11}N_4$], (c) A dilactone (XI), $C_{24}H_{28}O_7$. (VIII) and (XI) were also obtained by further oxidation of the glycol (VI) under the same conditions. The infra-red spectrum of VIII (2.98, 3.7-4.0, 5.73, 5.88 μ), showed that it contained two 6-membered lactones one of which is probably hydroxy-lactone. From the spectral data of XI (5.67 and 5.77 μ) it must also contain two lactone rings, one of which is the original 6-membered lactone and the other a newly formed 5-membered one. Hydrolysis of obacunone with dil. alkali gave obacunoic acid (XII), $C_{26}H_{32}O_8$, the I.R. absorption of which clearly indicated the presence of an hydroxyl, a maximum of this compound (U.V. 210 mμ (ε 11,600)) suggested that it must be a β-monosubstituted-α,β-unsaturated carboxylic acid. The hydroxyl group in XII was believed to be tertiary, since it resisted chromic

1960

SCHEME 1



oxide oxidation under various conditions. An attempted acetylation (by the pyridine or sodium acetate method), however, gave rise to an isomeric carboxylic acid (XIII), $C_{26}H_{32}O_8$. XIII was also obtained by merely boiling XII in pyridine. The infra-red spectrum of XIII showed no absorption bands corresponding to an hydroxyl, an acetyl or a double bond conjugated with a carboxyl group. In the ultra-violet spectrum the intensity of the maximum at 210 mμ had fallen to 6,600, almost half of the original value. These facts indicated the disappearance of α,β-unsaturation. The above date could be properly interpreted by assuming the presence of an α,β-unsaturated 7-membered lactone ring in obacunone.

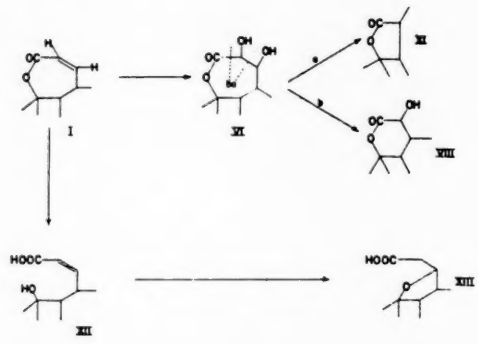


FIG. 1.

This assumption received further support from the observation that obacunone and ethioobacunoic acid [iii(b) and iii(c)] show extremely facile hydrolysis of the 7-membered lactone when the α.β-unsaturation is removed.

(iii) The relationship between the furan, 6-membered and 7-membered lactone rings

For the following reasons the three rings are placed as shown in I

(Fig. 2): namely, the furan ring is joined to the 6-membered lactone which has an ether linkage in the α-position to the carbonyl, while the 7-membered lactone is not directly linked to the other two rings.

(a) (Scheme 1 and Fig. 2). The previously described dilactone XI, one of whose lactones is 6-membered, inherited form the presurser, and the other 5-membered newly formed by oxidation, was hydrogenated in AcOH solution over Pd/C to give a neutral compound XIV, $C_{24}H_{32}O_7$, and a carboxylic acid XV, $C_{24}H_{34}O_7$. Bands corresponding to a furan ring were absent from the I.R. spectrum of XIV indicating the saturation of this ring. The infra-red spectra of XV (I.R. 5.72, 5.90 μ in Nujol; 5.69 μ in $CHCl_3$) and its ester XVI (I.R. 5.73, 5.89 μ in Nujol; 5.70 μ in $CHCl_3$) indicated that the 6-membered lactone present in the precurser, which was activated by the furan ring, had been hydrogenolysed but that the 5-membered lactone had survived.

(b) (Scheme 2 and Fig. 2). Methyl hydrogenoctahydroobacunoninate XVIII, $C_{27}H_{42}O_8$,[5] obtained by hydrogenation of methyl obacunoate (XVII) in

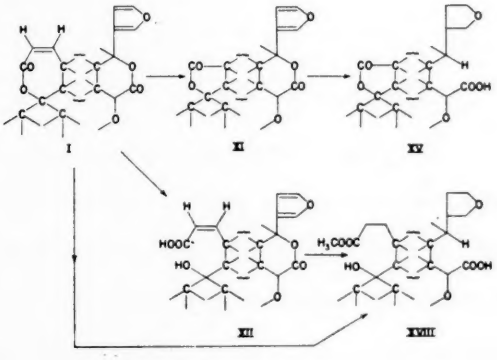
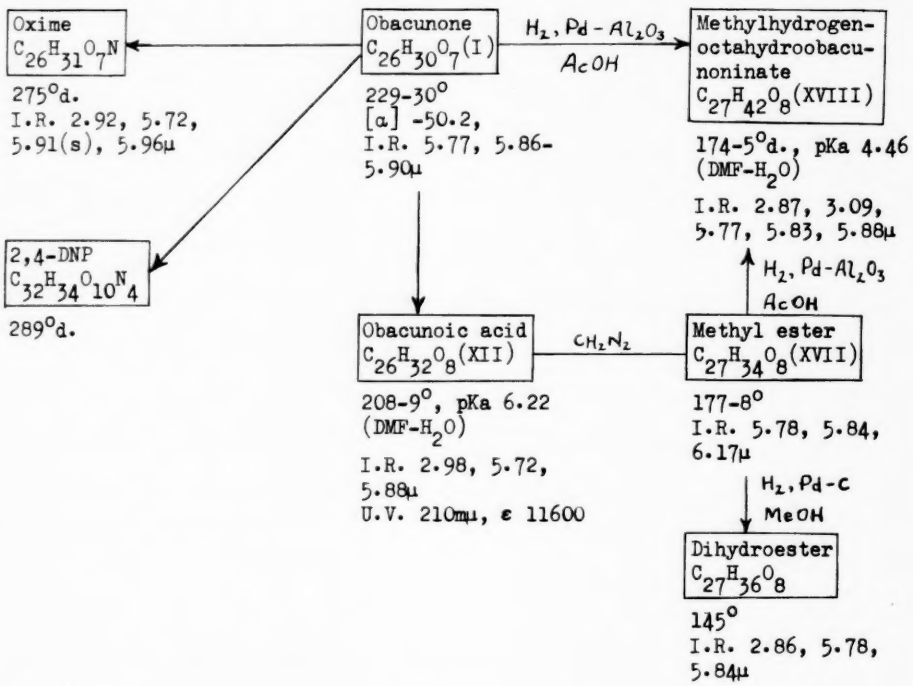


FIG. 2.

AcOH solution over $Pd\text{-}Al_2O_3$, was also formed by hydrogenation of obacunone itself in the same way, followed by crystallization from methanol. These facts can be interpreted as hydrogenolysis of the 6-membered lactone due to

SCHEME 2



activation by the furan ring, in the first case, but the latter involves, in addition to the hydrogenolysis, methanolysis of the saturated 7-membered lactone [see also iii(c)].

The unusually high acidity (Table 1) of the carboxylic acids XV and XVIII suggests that there may be an electron-withdrawing group (probably an ether group) located on the α-carbon atom to the carboxyl group which was generated during hydrogenolysis.

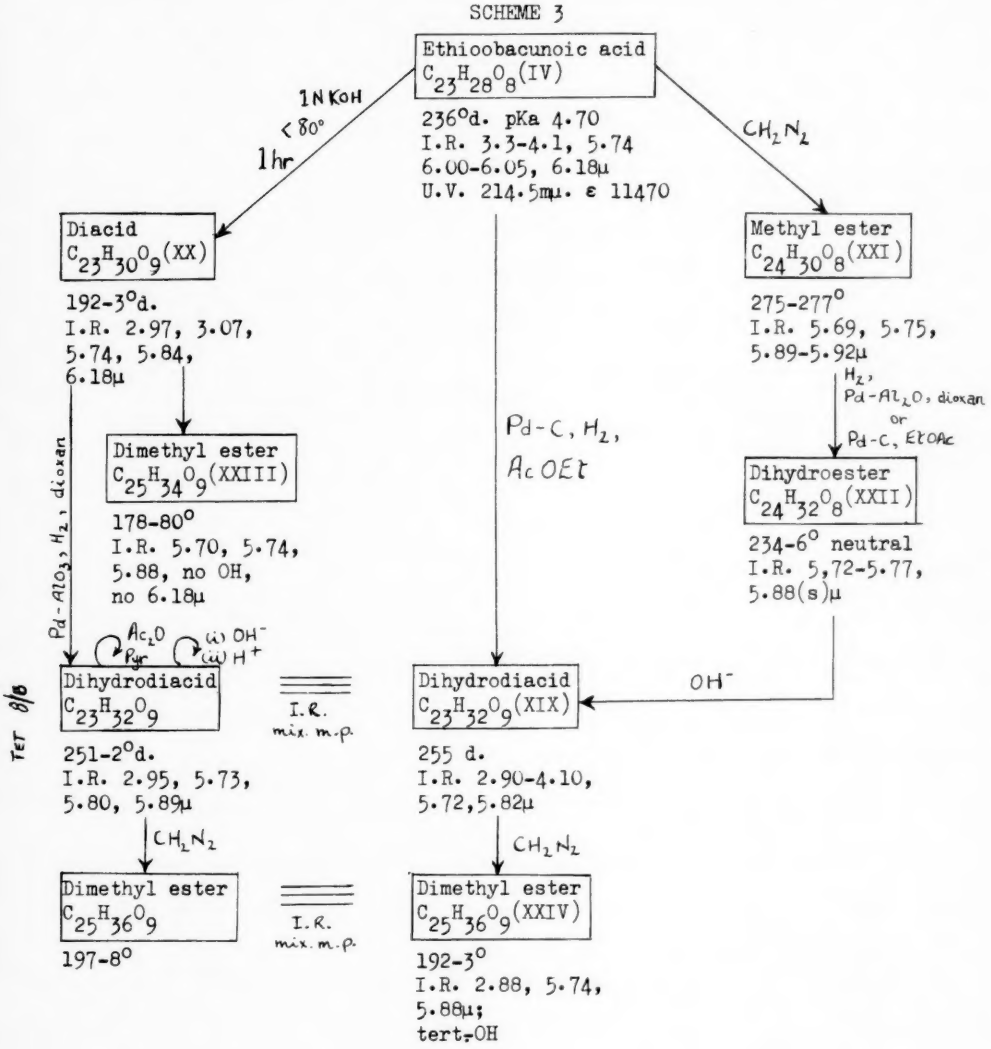
TABLE 1. pKa Values of Carboxylic Acids in 50% DMF-H_2O

CH_3COOH 6.52; C_6H_5COOH 6.12; obacunoic acid (XII) 6.22: acid (XV) 4.90; acid (XVIII) 4.46; acid (XVIII) 2.9;* hexahydrolimonic acid 2.7;* ethioobacunoic acid (IV) 4.67.

* in H_2O

(c) (Scheme 3 and Fig. 3). Ethioobacunoic acid (IV) absorbed 1 mole

SCHEME 3



of hydrogen in AcOH solution over Pd/C to give the dihydro-dicarboxylic acid XIX $C_{23}H_{32}O_9$. This compound had an hydroxyl group which resisted acetylation, and showed tribasisity under normal titration conditions. The same compound XIX was also obtained by two different methods. (1) Treatment of IV with 1 N KOH solution to give an unsaturated dicarboxylic acid XX, $C_{23}H_{30}O_9$, which on sequent hydrogenation over Pd-Al_2O_3, yielded XIX. (2) Under the same hydrogenation the methyl ester of IV (XXI, $C_{24}H_{30}O_8$) gave a neutral dihydro-ester XXII, $C_{24}H_{32}O_8$, which was, in turn, hydrolysed to give XIX. Apparently the reduction of ethioobacunoic acid (IV) to the dihydrodicarboxylic acid XIX involves only the saturation of an α,β-unsaturated 7-membered lactone and subsequent facile hydrolysis of the resulting saturated lactone, but not the hydrogenolysis of the 6-membered lactone. The stability of the 6-membered lactone in this case was attributed to the lack of furan ring activation.

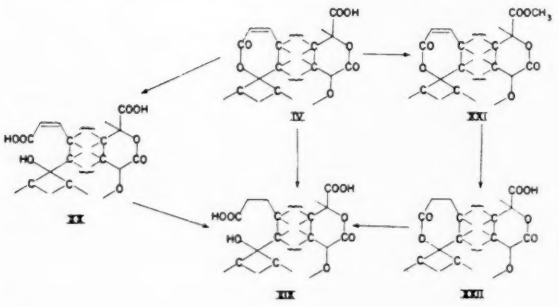


FIG. 3.

The low pKa value (see Table 1) of ethioobacunoic acid (IV) also lends support to the assignment of a carboxyl group, as indicated in IV.

The tertiary character of the hydroxyl group present in dihydro-dicarboxylic acid XIX, obtained from the opening of the 7-membered lactone, in obacunoic acid (XII) and XX was indicated by the following observations. (1) With acetic anhydride in pyridine XIX gave unchanged starting material, and XII gave rise to a new tetrahydrofuran group (XIII) instead of an acetate. (2) An attempted methylation of XX with CH_2N_2 gave a dimethyl ester with simultaneous loss of the hydroxyl band in the I.R. absorption. (3) The resistance of XII to oxidation with chromic acid.

And the evidence that this tertiary hydroxyl group in XIX is attached to CMe_2 group was presented by the following experiments: when the dimethyl ester (XXIV) was treated by phosphoroxychloride in pyridine or potassium hydrogensulfate in acetic anhydride, the dehydro-dimethylester (XXV),

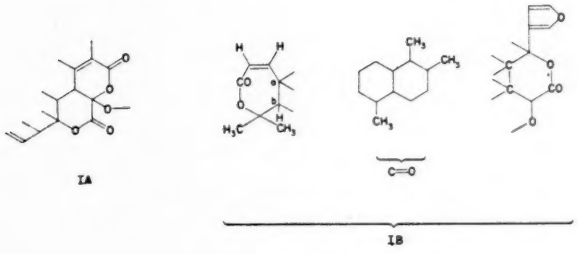


FIG. 4.

$C_{25}H_{34}O_8$, m.p. 149-151°C was obtained. With ozone XXV gave acetone (identified as 2,4-dinitrophenylhydrozone) and neutral crystalline compound m.p. 144-146°C.

The above results can be summarized as IB. Since the 7-membered lactone ring could be formed from the A-ring of lanostanone by Arigoni-type oxidation,[6] it might be thought that two carbon atoms (a and b in IB) of 7-membered lactone ring belong to the hydronaphthalene ring.

---

[6] D. Arigoni, D.H.R. Barton, R. Bernaseoni, C. Djerassi, J.S. Mills and R. Wolf, Proc. Chem. Soc. 306 (1959).

Tetrahedron Letters No. 8, pp. 11-13, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

dl-18-NORTESTOSTERONE

William S. Johnson and Kenneth V. Yorka

Department of Chemistry, University of Wisconsin, Madison, Wisconsin

(Received 12 March 1960)

IN view of the therapeutic importance of 19-nor steroidal hormones, there has recently been considerable interest in examining the 18-nor compounds. To date 18-nor-estrone,[1] -progesterone,[2] and -cortisone[3] have been prepared, but no representative of the male hormone series has been reported. We disclose herewith a total synthesis of racemic 18-nortestosterone (VI).

The cis-anti-trans alcohol I,[4] on reduction with lithium and alcohol in ammonia followed by hydrolysis of the enol ether and catalytic reduction of the resulting unsaturated ketone, was converted stereoselectively into dl-3α-hydroxy-18-nor-D-homoetiocholane-17a-one (II).[5] Contraction of ring-D was effected by the following sequence. The hydroxy ketone II was converted into the 17-furfurylidene derivative[5] which, as the 3-acetate, m.p. 194-195°

TET 8/8+

---

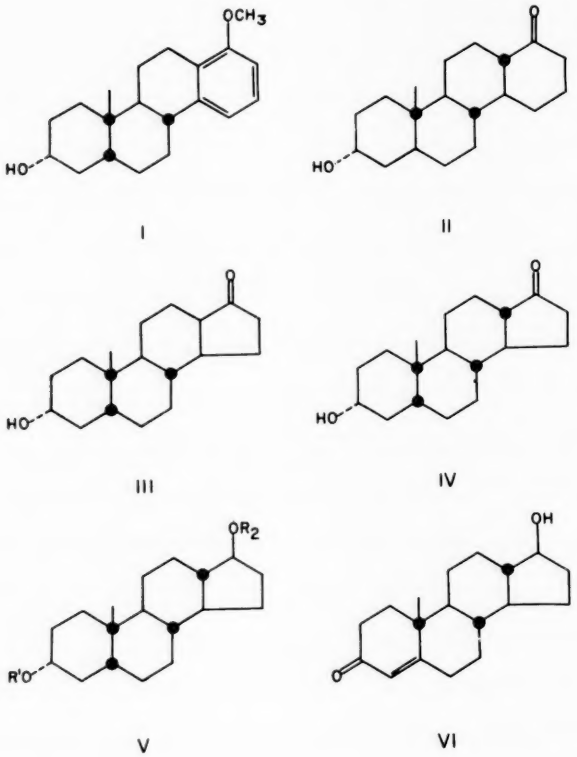
[1] K.H. Loke, G.F. Marrian, W.S. Johnson, W.L. Meyer and D.D. Cameron, Biochim. Biophys. Acta 28, 214 (1958).

[2] R. Anliker, M. Müller, M. Perelman, J. Wohlfahrt and H. Heusser, Helv. Chim. Acta 42, 1071 (1959).

[3] L. Velluz, G. Amiand, R. Heymes and B. Goffinet, C.R. Acad. Sci. Paris 250, 371 (1960).

[4] W.S. Johnson, A.D. Kemp, R. Pappo, J. Ackerman and W.F. Johns, J. Amer. Chem. Soc. 78, 6312 (1956).

[5] W.S. Johnson, W.A. Vredenburgh and J.E. Pike, J.Amer.Chem.Soc. In press.



(C, 76.2; H, 8.3), was ozonolyzed to give dl-3α-acetoxy-18-nor-etiohomobilianic acid, m.p. 213-214° (C, 66.2; H, 8.2). This diacid was transformed, with diazomethane, into the dimethyl ester, m.p. 111-112° (C, 67.5; H, 8.8) which was cyclized with potassium t-butoxide in benzene.[6] Hydrolysis and decarboxylation of the resulting β-keto ester was effected by heating in triethylene glycol containing about 5% water which yielded a mixture of two epimeric

---

[6] W.S. Johnson, B. Bannister and R. Pappo, J. Amer. Chem. Soc. 78, 6331 (1956).

1960

(at C_{13}) hydroxy ketones: m.p. 150-151° (C, 78.2; H, 10.25), acetate, m.p. 144-145° (C, 75.5; H, 9.55); and m.p. 113-114° (C, 78.3; H, 10.3), acetate, m.p. 116-117° (C, 75.5; H, 9.6). The configurations of these substances were established by reduction experiments with pyridine-borane in acetic acid.[7] This regent, which was shown to reduce the 17-carbonyl group of epiandrosterone acetate in high yield, similarly effected complete reduction of the keto group of the 117° acetate, but was completely inert to the 145° acetate. The latter therefore corresponds to the 13-iso compound III with a hindered (axial to ring C) keto group, while the former corresponds to the isomer of natural configuration IV, and its reduction product is, accordingly, dl-3α-acetoxy-17β-hydroxy-18-noretiocholane (V,R^1 = Ac,R^2 = H). Benzoylation afforded the 17-benzoate V (R^1 = Ac, R^2 = COC_6H_5), m.p. 144-145° (C, 76.6; H, 8.7) which on mild saponification yielded the hydroxy benzoate V (R^1 = H, R^2 = COC_6H_5), m.p. 132-133° (C, 78.4; H, 9.0). Chromic acid oxidation to the 3-keto compound, m.p. 139-140° (C, 78.7; H, 8.3) followed by bromination and dehydrobromination afforded the benzoate of dl-18-nortestosterone, m.p. 151-152° (C, 79.3; H, 8.0), saponification of which gave dl-18-nortestosterone (VI), m.p. 165-167° (C, 79.2; H, 9.6). The results of physiological tests will be reported elsewhere.

The 18-nor-17-keto compounds III and IV are readily interconverted. The position of the equilibrium of the hydroxy ketones in dioxane and hydrochloric acid was estimated, by infrared spectroscopy, to be about 60-65% in favor of the cis isomer. The interconvertibility of these isomers make the above synthesis completely stereoselective, since pyridine-borane reduces only the trans isomer.[8]

---

[7] R.P. Barnes, J.H. Graham and M.D. Taylor, J.Org.Chem. 23, 1516 (1958).

[8] This work was aided by grants from the U.S. Public Health Service and the National Science Foundation.

Tetrahedron Letters No. 8, pp. 14-15, 1960. Pergamon Press Ltd. Printed in Great Britain.

SYNTHESIS OF A BOREPIN

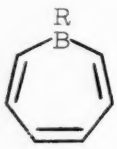
E. E. van Tamelen, G. Brieger and K. G. Untch

Department of Chemistry, University of Wisconsin

Madison, Wisconsin

(Received 14 March 1960)

Theoretical considerations[1] permit the conclusion that borepin (1-boro-2.4.6-cycloheptatriene) (Ia-Ib), in which neutral trivalent

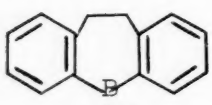


Ia

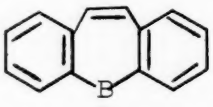
Ib

boron is incorporated into a cyclic molecular orbital of six electrons, should possess aromatic stability. We provide herein the first example of this heterocyclic system.

The anhydride of the borinic acid II, prepared by reaction of



II



III

o,o'-dilithiobibenzyl and tributyl borate according to the method of

---

[1] E. Hückel, Grundzüge der Theorie ungesättigter und aromatischer Verbindungen. Verlag Chemie, Berlin, 1938, pp. 71-85.

1960

Letsinger and Skoog,[2] was converted by means of N-bromosuccinimide to an intermediate bromo substitution product, which without purification was dehydrohalogenated with methanolic sodium methoxide. The resulting dibenzoborepin III (X = OH) was isolated as the ethanolamine derivative (IIIa), m.p. 222-226° (Calcd: C, 77.1; H, 6.4; N, 4.4. Found: C, 77.1; H, 6.6; H, 4.3. λ_{max}^{EtOH} 227, 298 mμ ε = 16,000, 8,230, resp.). The structure of III was established through degradation to cis-stilbene by means of ammoniacal silver nitrate,[3] which reagent transforms the starting dihydro compound II to bibenzyl. Lithium aluminum hydride converts[4] IIIa to a product--isolated as the low-melting, unstable pyridine complex--regarded as the parent borane (III, X = H), on the basis of (i) its BH absorption at 4.32 microns, and (ii) the acid-promoted hydrolytic oxidation to the starting borinic acid (III, X = OH), isolated and identified as IIIa.

Aromatization by means of N-bromosuccinimide, and protection of intermediates as borinic acids, are being applied in this Laboratory to the preparation of simpler members of the borepin family.

TET 8/6

This research was supported by grants from the Petroleum Research Foundation and the Wisconsin Alumni Research Foundation.

---

[2] R. Letsinger and I. Skoog, J. Am. Chem. Soc. 77, 5175 (1955).

[3] A. Michaelis and M. Behrens, Ber. 27, 244 (1894).

[4] M. F. Hawthorne, J. Am. Chem. Soc. 80, 4293 (1958).

Tetrahedron Letters No. 8, pp. 16-19, 1960. Pergamon Press Ltd. Printed in Great Britain.

THE ABSOLUTE CONFIGURATION OF (+)-3-METHYL-3-t-BUTYL-1-CHLOROALLENE

Ernest L. Eliel

Department of Chemistry, University of Notre Dame,

Notre Dame, Indiana

(Received 13 February 1960; in revised form 7 March 1960)

SINCE the absolute configuration of (+)-tartaric acid was established by Bijvoet et al.,[1] the configuration of any other compound containing one or more asymmetric carbons may, in principle, be established by correlation with (+)- or (-)-tartaric acid. One of the remaining general problems of static stereochemistry is the assignment of configuration to optically active compounds not containing asymmetric atoms. For the case of dissymmetric biphenyls, this problem has been solved elegantly by Mislow and by Berson and their coworkers.[2] The correlation with centroasymmetric compounds they obtained necessarily rests on mechanistic arguments. We wish now to present a similar argument which suggests the (R)-configuration[3] for (+)-3-methyl-3-t-butyl-1-chloroallene (I, Fig. 2),[4] a representative of the class of dissymmetric allenes.

---

[1] J.M. Bijvoet, A.F. Peerdeman and A.J. van Bommel, Nature, Lond. 168, 271 (1951); see also W.W. Wood, W. Pickett and J.G. Kirkwood, J. Chem. Phys. 20, 561 (1952).

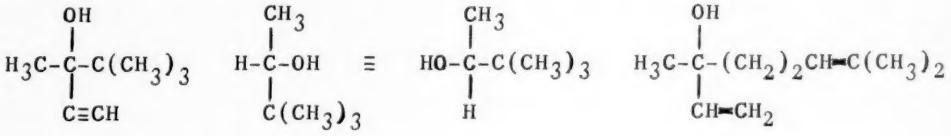
[2] cf. K. Mislow, Angew. Chem. 70, 683 (1958).

[3] cf. R.S. Cahn, C.K. Ingold and V. Prelog, Experientia 12, 81 (1956).

[4] S.R. Landor and R. Taylor-Smith, Proc. Chem. Soc. 154 (1959).

1960

(+)-I was synthesized by Landor and Taylor-Smith[4] from (+)-methylethynyl-t-butyl carbinol (II) and thionyl chloride. To deduce from this the configuration of (+)-I, one must first assign configuration to (+)-II. This could be done on the basis of arguments presented by Brewster[5] if one knew the polarizability sequence of the groups ethynyl, methyl, t-butyl and hydroxyl. Of these groups, ethynyl undoubtedly has the highest polarizability.[5] The polarizability order of the remaining three groups may be deduced from the fact[6] that (+)-pinacolyl alcohol (III) (in which the hydrogen is the substituent of lowest polarizability) has the D- or (S)-configuration as shown in Fig. 1. In its simplest form, the argument



(S)-(+)-II (S)-(+)-III (R)-(+)-IV

FIG. 1.

is that since the ethynyl group in II is the group of highest polarizability whereas the hydrogen in III is the group of lowest polarizability, the other three substituents in II and III being the same, therefore (+)-II and (+)-III must have the opposite arrangement of groups (ethynyl taking the place of hydrogen).

---

[5] J.H. Brewster, J. Amer. Chem. Soc. 81, 5475 (1959).

[6] H.S. Mosher and E. La Combe, J. Amer. Chem. Soc. 72, 3994 (1950); cf. J.A. Mills and W. Klyne in Progress in Stereochemistry Vol. 1, p. 201 (Edited by W. Klyne). Butterworths, London (1954).

[That the configurational symbol for (+)-II and (+)III is the same - (S) - is a consequence of the nomenclature sequence rule[3] and is immaterial to the argument.] It may be worth mentioning that the configuration of (+)-II so assigned corresponds to the known[7] configuration of (+)-linalool (IV), isohexenyl taking the place of t-butyl.

Landor and Taylor-Smith[4] associated an S_Ni' mechanism[8] with the stereospecific conversion of (+)-II to (+)-I. If this is accepted, the configuration of (+)-I is (R), as shown in Fig. 2 (right-hand side), because as cyclic transition state (or its ion pair equivalent) is involved in the S_Ni' mechanism.[9] A plausible alternative to the S_Ni' path would seem to be an S_N2' mechanism[8] (Fig. 2, left-hand side). Fortunately, this should also give rise to (R)-3-methyl-3-t-butyl-1-chloroallene, since the S_N2' mechanism has been shown[10] to involve a double inversion.

The assumptions involved in the assignment of the (R)-configuration to (+)-I are as follows: (I) (+)-II has the (S)-configuration (Fig. 1). (2) The conversion of (+)-II to (+)-I proceeds by either an S_Ni' or an S_N2' mechanism. (3) The stereochemistry of the S_N2' mechanism is as shown (Fig. 2).

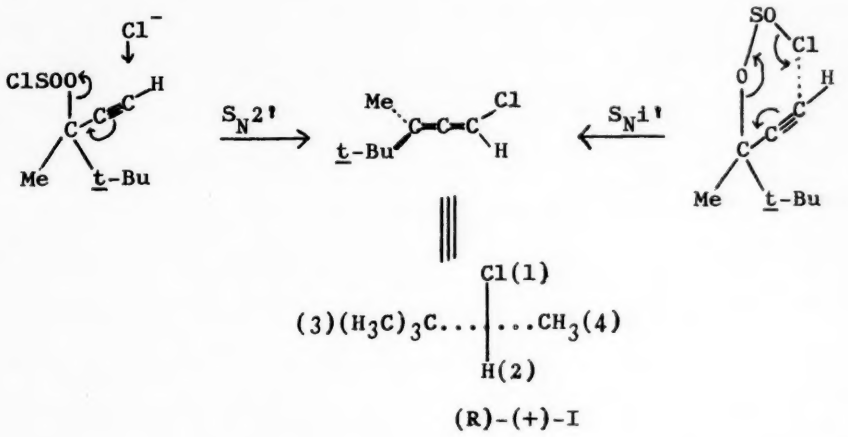
---

[7] V. Prelog and W. Eiji, Liebigs Ann. 603, 1 (1957). Actually it was shown that (-)-linalool has the (S)-configuration.

[8] cf. R.H. DeWolfe and W.G. Young, Chem. Rev. 56, 814,769 (1956).

[9] H.L. Goering, T.D. Nevitt and E.F. Silversmith, J. Amer. Chem. Soc. 77, 4042 (1955); F.D. Caserio, G.E. Dennis, R.H. DeWolfe and W.G. Young, Ibid. 77, 4182 (1955).

[10] G. Stork and W.N. White, J. Amer. Chem. Soc. 78, 4609 (1956).



(R)-(+)-I

FIG. 2.

We believe these assumptions are reasonable and likely to be correct. If they are not, the argument presented is obviously no longer cogent even though it may fortuitously give the right answer.

Tetrahedron Letters No. 8, pp. 20-22, 1960. Pergamon Press Ltd. Printed in Great Britain.

ORGANIC FLUORINE COMPOUNDS[1]

FLUORINE DERIVATIVES OF MEVALOLACTONE

E. D. Bergmann and S. Cohen*

Department of Organic Chemistry, Hebrew University, Jerusalem

(Received 17 March 1960)

THE substitution of hydrogen by fluorine transforms in some cases a metabolite into an anti-metabolite; in others, it produces a substance which can be incorporated by the cell instead of the "normal" compound. In view of the fundamental role of mevalonic acid and its lactone in biosynthetic processes, fluorine derivatives of mevalolactone would appear to be almost of equal interest if either of these two alternatives applies.

The diethyl ketal of ethyl γ-fluoroacetoacetate[2] [b.p. 63-64° (0.5 mm)] (Found: C, 54.2; H, 8.6. $C_{10}H_{19}FO_4$ requires C, 54.1; H, 8.6) was reduced by lithium aluminium hydride to the diethyl ketal of 4-fluoro-3-oxobutanol $FCH_2COCH_2CH_2OH$. The attempt to produce the free keto alcohol, however, led only to polymeric material. The alkali-catalysed condensation of fluoroacetone[3] with formaldehyde, on the other hand, gave in 43% yield a very stable fluoro-3-oxobutanol, b.p. 57-58° (0.5 mm) (Found: C, 45.8; H, 6.5; F, 18.2. C_4H_7FO

---

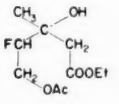
* Israel Institute of Biological Research, Ness Ziona.

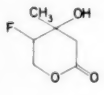
1 See E.D. Bergmann and I. Shahak, J. Chem. Soc. In press (1960).

2 E.D. Bergmann, S. Cohen and I. Shahak, J. Chem. Soc. 3278 (1959).

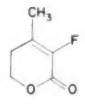
3 E.D. Bergmann and S. Cohen, J. Chem. Soc. 2259 (1958).

requires: C, 45.3; H, 6.6; F, 17.9), which thus appears to be the 2-fluoro-derivative $CH_3CO.CHF.CH_2OH$. It is not unreasonable to assume that, as in many other cases, the methylene group of fluoro-acetone would react in preference to the methyl group, especially as this also applies to the parallel reaction of chloroacetone.[4] 2-Fluoro-3-oxobutylacetate [b.p. 54-55° (0.6 mm)] reacted normally with ethyl bromoacetate and zinc in ether to give in 55% yield ethyl δ-acetoxy-γ-fluoro-β-hydroxy-β-methylvalerate (I), b.p. 124-125° (0.4 mm) (Found: C, 51.0; H, 7.4; F, 8.4. $C_{10}H_{17}FO_5$ requires C, 50.9; H, 7.2; F, 8.0). Hydrolysis of (I) gave in 27% yield γ-fluoromevalolactone (II), b.p. 124-125° (0.4 mm) (Found: C, 49.2; H, 6.2; F. 13.4. $C_6H_9FO_3$ requires C, 48.6; H, 6.1; F, 12.9).[5,6]


I


II

V


VI

VII

For the preparation of α-fluoromevalolactone (V) the observation has been utilized that the surprisingly stable enolate of ethyl fluoroacetate[7]

---

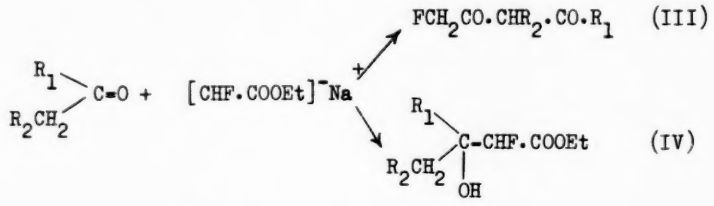
[4] E.R. Buchman and H. Sargent, J. Amer. Chem. Soc. 79, 400 (1945).

[5] So far, we have not determined whether the product is sterically homogeneous.

[6] This synthesis is modelled on the method of Folkers et al. for the preparation of mevalolactone. J. Amer. Chem. Soc. 79, 2316 (1957).

[7] E.D. Bergmann and S. Szinai, J. Chem. Soc. 1521 (1956).

reacts with ketones in two ways, viz., in a Claisen condensation, yielding 1-fluoro-2,4-diketones (III) and by a ketol condensation, yielding esters of α-fluoro-β-hydroxy acids (IV):



3-Oxobutyl acetate reacts according to the second mechanism, yielding directly α-fluoromevalolactone (V) via (IV, R_1 = $-CH_2CH_2OAc$, R_2 = H). Unfortunately, (V) could not be obtained in pure form; upon distillation [b.p. 120-123° (0.2 mm)] it loses water and gives the corresponding unsaturated lactone (VI) (Found: C, 55.8; H, 5.6; F, 14.3. C_6H_7FO requires C, 55.4; H, 5.4; F, 14.6).

The infra-red spectra, which will be reported in a more detailed communication, support the formulae of the substances described. The compounds (II) and (V) are now being studies as to their biological properties.

A third fluoromevalolactone (VII) has been studied by Singer et al.,[8] but its synthesis has not yet been published.

Acknowledgment - This study was initiated at the Biochemistry Department, College of Physicians and Surgeons, Columbia University, New York. One of us (E.D.B.) is deeply grateful to Professor David Rittenberg, Head of the Department, for the hospitality afforded to him.

---

[8] F.M. Singer, J.P. Januszka and A. Berman, Proc. Soc. Exp. Biol.Med. 102, 170 (1959).

Tetrahedron Letters No. 8, pp. 23-24, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

GEOMETRICAL ISOMERS OF STIBINOUS AND STIBINIC PROPENYL COMPOUNDS

A. N. Nesmeyanov, A. E. Borisov and N. V. Novikova

U.S.S.R. Academy of Sciences, Moscow

(Received 10 March 1960)

IN continuation of stereochemical investigation of organometallic alkenyl compounds syntheses of a number of geometrical isomers of stibinous and stibinic propenyl compounds have been effected.

Cis- and trans-lithiumpropenyl react with stibinous chloride to form cis- and trans-tripropenyl stibine, respectively.

$$3CH_3CH{=}CHLi + SbCl_3 \longrightarrow (CH_3CH{=}CH)_3Sb + 3LiCl$$

The reaction of the isomers with halogens leads to a series of isomeric stibinic compounds.

$$(CH_3CH{=}CH)_3Sb + X_2 \longrightarrow (CH_3CH{=}CH)_3SbX_2 \; ; \; X{=}Cl,Br,J$$

The same compounds, cis- and trans- respectively, have been isolated by the reaction of cis- and trans-propenyl stibine with thallic chloride.

Cis-propenylstibine bromide and chloride are crystallinic solids, and the trans-isomers are liquids.

The liquid geometrical isomers of pentapropenyl stibine have been prepared by the reaction of cis- and trans-tripropenylstibine dibromide and the corresponding isomers of lithiumpropenyl.

$$(CH_3CH{=}CH)_3SbBr_2 + 2CH_3CH{=}CHLi \longrightarrow (CH_3CH{=}CH)_5Sb + 2LiBr$$

These differ by the refractive index (cis-compound n_D^{20} 1.5610, trans-

compound n_D^{20} 1.5490) and the infra-red spectra.

Two tetrapropenylstibonium bromide isomers with different melting points (cis-compound m.p. 140-143°, trans-compound m.p. 45-48°) and infra-red spectra have been prepared by treatment of these isomers with the definite quantity of bromine.

NN	Compounds	Infra-red spectra in cm^{-1}	
		cis	trans
1	$(CH_3CH=CH)_3Sb$	920 w, 970 w, 1182 m, 1615 m	935 m, 970 s, 1068 m, 1200 s, 1620 s
2	$(CH_3CH=CH)_3SbCl_2$	923 w, 1200 w, 1600 w	955 s, 1070 m, 1188 s, 1615 s
3	$(CH_3CH=CH)_3SbBr_2$	925 w, 1600 w	953 s, 1068 m, 1188 s, 1620 s
4	$(CH_3CH=CH)_4SbBr$	925 w, 1600-1610 m	965 s, 1068 s, 1190 s, 1620 s
5	$(CH_3CH=CH)_3SbJ_2$	928 w, 1470 s, 1610 m	948 s, 1065 m, 1625 s
6	$(CH_3CH=CH)_5Sb$	920 w, 974 w, 1200 w, 1595 s	972 s, 1068 m, 1185 m, 1600 s

s - strong, m - middle, w - weak

The configurations of the compounds prepared were assigned on the basis of infra-red analysis and are in agreement with the regularity drawn by us.[1]

[1] A.N. Nesmeyanov and A.E. Borisov, Dokl. Akad. Nauk SSSR 60, 67 (1948); A.N. Nesmeyanov, A.E. Borisov and N.V. Novikova, Dokl. Akad. Nauk SSSR 119, 504 (1958); A.N. Nesmeyanov, A.E. Borisov and N.V. Novikova, Izv. Akad. Nauk SSSR, Otdel. khim. nauk 1216 (1959).

Tetrahedron Letters No. 8, pp. 25-27, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

ÜBER DIE IDENTITÄT VON RUTILANTINON MIT PYRROMYCINON UND ÜBER DIE LAGE DER CARBOMETHOXY-GRUPPE IN PYRROMYCINONEN

H. Brockmann,[1] H, Brockmann,Jr[1] J. J. Gordon,[2]
W. Keller-Schlierlein,[3] W. Lenk,[1] W. D. Ollis,[4] V. Prelog,[3]
and I. O. Sutherland.[4]

(Received 10 March 1960)

AUS den Kulturbrühen gewisser Actinomyces-Stämme wurde eine Verbindung $C_{22}H_{20}O_9$ isoliert, die den Namen ε-Pyrromycinon[5] erhielt. Dieselbe Verbindung kommt glykosidisch gebunden in Pyrromycin[6] und in den Antibiotica Cinerubin A und B[7] vor. Auf Grund der physikalischen Eigenschaften und des chemischen Verhaltens wurde für das ε-Pyrromycinon[5,7] die Konstitutionsformel I vorgeschlagen. Kurz nach der Veröffentlichung dieser Ergebnisse wurde als Aglykon weiterer Antibiotica aus Actinomyces-Kulturen eine Verbindung der gleichen Zusammensetzung, das Rutilantinon, beschrieben, für welches die Formel II

---

[1] Organisch-chemischen Institut der Universität, Göttingen.

[2] Antibiotics Research Station, Medical Research Council, Clevedon.

[3] Organisch-chemischen Laboratorium der Eidg. Technischen Hochschule, Zürich.

[4] University of Bristol.

[5] H. Brockmann und W. Lenk, Chem. Ber. 92, 1880 (1959).

[6] H. Brockmann und W. Lenk, Chem. Ber. 92, 1904 (1959).

[7] L. Ettlinger, E. Gäumann, R. Hutter, W. Keller-Schierlein, F. Kradolfer, L. Neipp, V. Prelog, P. Reusser und H. Zähner, Chem. Ber. 92, 1867 (1959).

abgeleitet wurde.[8] Die ähnlichen Eigenschaften des ε-Pyrromycinons und des Rutilantinons regten zu einem direkten Vergleich der beiden Verbindungen und ihrer Derivate an, der in Bristol, Göttingen und Zürich durchgeführt wurde und zum eindeutigen Schluss führte, dass sie identisch sind. Die IR.-Absorptionsspektren des Rutilantinons, des Tetraacetyl-rutilantinons und des Bisanhydro-rutilantinons waren praktisch identisch mit denjenigen der entsprechenden Verbindungen der Pyrromycinon-Reihe und die entsprechenden Verbindungspaare zeigten keine Smp.-Erniedrigung.[9]

Es blieb noch die Aufgabe übrig, die Diskrepanz in den Konstitutionsformeln zu beseitigen. Während die Lokalisierung der Carbomethoxy-Gruppe in ε-Pyrromycinon nur auf einem "Indizien-Beweis" beruhte,[5] wurde sie im Rutilantinon durch Oxydation des Bisanhydro-rutilantinons III (identisch mit η-Pyrromycinon[5]) mit Kaliumpermanganat zu Benzol-tetracarbonsäure-(1,2,3,4) (IV) auf eindeutige Weise festgelegt.[8] Die Wiederholung dieser Oxydation mit authentischem η-Pyrromycinon, sowie die Oxydation des Bisanhydro-aglykons aus Cinerubinen mit Salpetersäure führte ebenfalls zur Säure IV. Diese wurde als Tetramethylester, durch Vergleich mit authentischen Vergleichspräparat identifiziert.

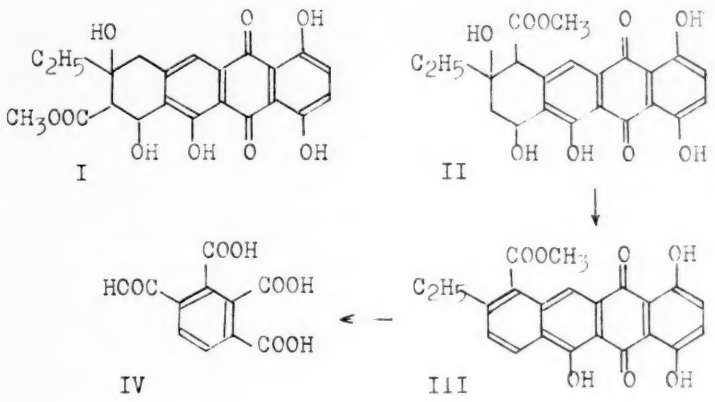
Die Lage der Äthyl-Gruppe in der Pyrromycinon-Reihe wurde durch die Verknüpfung mit der Rhodomycinon- bzw. Isorhodomycinon-Reihe und oxydativen

---

[8] W.D. Ollis, I.O. Sutherland und J.J. Gordon, Tetrahedron Letters No. 16, 17 (1959).

[9] Der grosse Unterschied bei den veröffentlichten Smp. von Tetraacetyl-rutilantinon (Smp. 250°)[8] und von Tetraacetyl-ε-pyrromycinon (Smp.219-221°[1] bzw. 203-210°)[7] beruht auf der verschiedenen Methodik der Smp. Bestimmung.

Abbau des Ringes A in der letzterwähnten Reihe zu β-Äthyl-adipinsäure beiwiesen.[10] Es besteht also kein Zweifel darüber, dass die Carbomethoxy-Gruppe die in Formel II dargestellte Lage besitzt.



[10] Unveröffenlichte Versuche von H. Brockman und Mitarb.

Tetrahedron Letters No. 8, pp. 28-34, 1960. Pergamon Press Ltd. Printed in Great Britain.

AKLAVINONE

J. J. Gordon

Antibiotics Research Station, Medical Research Council, Clevedon

L. M. Jackman

Imperial College of Science and Technology,
South Kensington, London S. W. 7

W. D. Ollis and I. O. Sutherland

University of Bristol

(Received 10 March 1960)

THE preceding communication describes the identity of rutilantinone (I), the aglycone of the rutilantins,[2] with ε-pyrromycinone,[3] which is

---

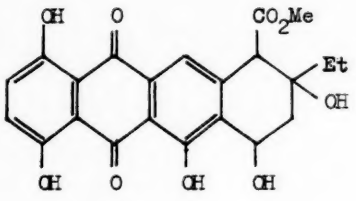
[1] H. Brockmann, H. Brockmann jnr., J. J. Gordon, W. Keller-Schlierlein, W. Lenk, W. D. Ollis, V. Prelog and I. O. Sutherland, Tetrahedron Letters No. 8, 25 (1960).

[2] W. D. Ollis, I. O. Sutherland and J. J. Gordon, Tetrahedron Letters No. 16, 17 (1959).

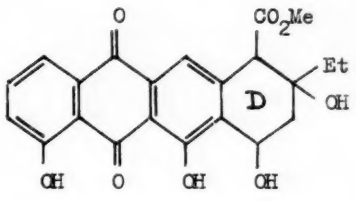
[3] H. Brockmann and W. Lenk, Chem. Ber. 92, 1880 (1959).

1960

similarly derived from the cinerubins[4] and pyrromycin.[5] We now wish to report on the structural relationship which has been shown to exist between ε-pyrromycinone (rutilantinone)(I) and aklavinone obtained from another antibiotic, aklavin.[6] Aklavinone ($C_{22}H_{20}O_8$) and rutilantinone ($C_{22}H_{20}O_9$) are shown to have closely analogous structures in that aklavinone just lacks one of the phenolic hydroxyl groups present in rutilantinone.



I



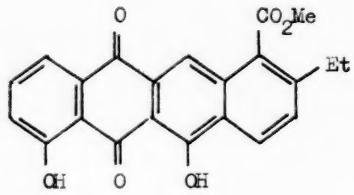
II

---

4 L. Ettlinger, E. Gäumann, R. Hütter, W. Keller-Schlierlein, F. Kradolfer, L. Neipp, V. Prelog, P. Reusser and H. Zahner, Chem. Ber. 92, 1867 (1959).

5 H. Brockmann and W. Lenk, Chem. Ber. 92, 1867 (1959).

6 F. Strelitz, H. Flon, U. Weiss and I.N. Asheshov, J. Bacteriol. 72, 90 (1956).



III

Mild acidic hydrolysis of aklavin hydrochloride yielded the aglycone, aklavinone, orange needles, m.p. 170° (Found: C, 64.15; H, 5.12; OMe, 7.47. $C_{22}H_{20}O_8$ requires C, 64.08; H, 4.89; (1) OMe, 7.53%) characterised (acetic anhydride-pyridine) as a tri-acetate, m.p. 198° (Found: C, 62.47; H, 5.16; OMe, 5.69. $C_{28}H_{26}O_{11}$ requires C, 62.45; H, 4.89; (1) OMe, 5.77%). Hydroxyl absorption [ν_{max} 3610 cm^{-1}. (Nujol)] in the infra-red spectrum of the tri-acetate indicated the presence of a tertiary hydroxyl group; and absorption in the carbonyl region was assigned to phenolic (ν_{max} 1785 cm^{-1}.) and alcoholic acetate (ν_{max} 1751 cm^{-1}.) groupings. Aklavinone was weakly acidic [pK_a' 9.9 (90% ethanol)]; it was converted into a dibasic acid [pK_a' 6.85 and 10.6 (90% aqueous acetone)] by alkaline hydrolysis. The presence of an ester group in aklavinone (probably $-CO_2Me$ by analogy with rutilantinone) was confirmed by the infra-red spectra of aklavinone

[ν_{max} 1728, 1740 cm^{-1}. (Nujol)] and its tri-acetate [ν_{max} 1740 cm^{-1}. (Nujol)].

The ultra-violet and visible spectra of aklavin,[6] aklavinone [λ_{max} (ε_{max}) 229 (43,800), 258 (26,700), 288 (11,500), 430 mμ (13,100), λ_{infl} 278 mμ (12,000) (in methanol)] and aklavinone tri-acetate [λ_{max} (ε_{max}) 214 (28,000), 259 (41,900), 340 mμ (7,100) (in ethanol)] were consonant with a 1:8-dihydroxyanthraquinone chromophore.[7] This assignment was further supported by the infra-red spectra of both aklavinone [ν_{max} 1674, 1623, 1575 cm^{-1}. (Nujol)] and its tri-acetate [ν_{max} 1681, 1600 cm^{-1}. (Nujol)].[8] These results led us to consider that aklavinone was a deoxy-rutilantinone and could be represented by structure (II).

Like rutilantinone, aklavinone was converted into a bisanhydro-derivative, orange needles, m.p. 236° (Found: C, 69.86; H, 4.22; OMe, 8.21. $C_{22}H_{16}O_6$ requires C, 70.20; H, 4.29; (1) OMe, 8.25%) by the action of toluenesulphonic acid in refluxing toluene. The spectral properties of this compound [ν_{max} 1740, 1678, 1627, 1602, 1579 cm^{-1}. (Nujol); λ_{max} (ε_{max}) 242 (45,100), 262 (47,400), 279 (19,300), 290 (19,600), 440 (18,900), 462 (14,600), 474 mμ (15,800) (in n-hexane)] are in accordance with its formulation as the 1:11-dihydroxytetracene-5:12-quinone derivative (III), the methoxycarbonyl and ethyl substituents being placed by analogy with bisanhydrorutilantinone and using biogenetic arguments similar to those used for ε-pyrromycinone (rutilantinone). This

---

[7] J. H. Birkinshaw, Biochem. J. 59, 485 (1955).

[8] H. Bloom, L. H. Briggs and B. Cleverley, J. Chem. Soc. 178 (1959).

structure (III) is further supported by the formation of benzene-1:2:3:4-tetracarboxylic acid, characterised as its tetramethyl ester, m.p. 130.5-131.5°, by alkaline permanganate oxidation of bisanhydroaklavinone, thus demonstrating that aklavinone has the structure (II).

The nuclear magnetic resonance spectrum of aklavinone ($CHCl_3$, 56.4 Mc.) exhibits the following bands (τ-values): 8.90 (3), 8.43 (2), 7.66 (2), 6.30 (3), 5.70 (1), 4.67 (1).* The first two bands show the characteristic pattern of an isolated ethyl group in which the two classes of protons are only slightly non-equivalent. The broad band at 7.66 clearly arises from a methylene group which cannot, however, be attached to an aromatic ring (α-protons in tetralin absorb at 7.30). The band at 6.30 is sharp and corresponds to an ester methyl group. The absorption near 4.67 consists of a broad band. Its position corresponds to the superimposition of two powerful deshielding effects and it must therefore be assigned to a proton attached to a carbon atom bearing both an aromatic ring and a hydroxyl group. The remaining band (5.70) is reasonably sharp and its position is consistent with an assignment to a proton which is simultaneously benzylic and α- to a carbomethoxy group. The lack of fine structure in this band indicates the absence of protons on the two adjacent carbon atoms.

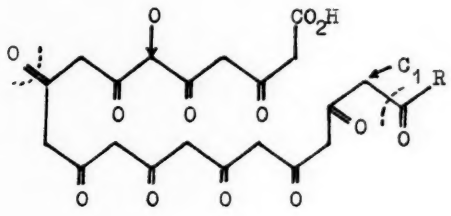
The assignments of the bands of the nuclear magnetic resonance spectrum of aklavinone can only be accommodated by the arrangement of substituents on ring D shown in formula (II). Thus the position of the

---

* The figures in parentheses refer to relative integrated intensities.

secondary hydroxyl group in aklavinone is settled and it may be presumed that the corresponding hydroxyl group is similarly located in rutilantinone. The position of the secondary hydroxyl group in ε-pyrromycinone (rutilantinone) was suggested previously only on a proposed biosynthetic scheme.[2,3,4]

The biogenetic route leading to aklavinone (see IV) may be considered to be the same as that leading to rutilantinone, except that p-oxidation, which leads to the extra hydroxyl group of rutilantinone, does not occur during the biosynthesis of aklavinone.



IV

Aklavin itself is amphoteric and appears to consist of a basic sugar (possibly $C_8H_{17}NO_4$ isomeric with amosamine[9] and mycaminose[10]) linked glycosidically to the secondary hydroxyl group of aklavinone.

---

9 C. L. Stevens, R. J. Gasser, T. K. Mukherjee and T. H. Haskell, J. Amer. Chem. Soc. 78, 6212 (1956).

10 F. A. Hochstein and P. P. Regna, J. Amer. Chem. Soc. 77, 3353 (1955).

We thank Professor W. Baker for his interest, and Mr. B. K. Kelly, the Director of the Antibiotics Research Station, Clevedon, and Dr. I. N. Asheshov for encouraging our collaboration.

1960

Tetrahedron Letters No. 9, pp. 1-4, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

SYNTHESIS OF A "MIXED-ACID" α-LECITHIN*

G. H. de Haas and L. L. M. van Deenen

Laboratory of Organic Chemistry, State University, Utrecht,

The Netherlands

(Received 15 March 1960)

SINCE naturally occurring glycerolphosphatides as a rule contain two different fatty acids, we have synthesized several "mixed-acid" α-lecithins. These synthetic lecithins may become valuable substrates for biochemical model studies.

The preparation of a number of L-α-lecithins containing two identical acyl groups by acylating L-α-glycerylphosphorylcholine with acyl chlorides of varying chain length (C_2 to C_{24}), has been reported.[1] The corresponding conversion of β-lysolecithins to lecithins with two different acyl groups proved possible as well.[2]

During our attempts to prepare defined "mixed-acid" lecithins from lysolecithins we succeeded in synthesizing γ-octadecanoyl-β-dodecanoyl-α-lecithin (IV) by another route.

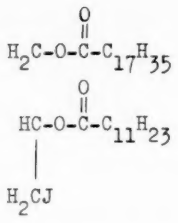
TET 9/A

---

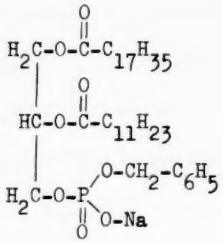
* This work is part of a study into the field of phosphatides initiated by the late Prof. F. Kögl.

1 N.H. Tattrie and C.S. McArthur, Canad. J. Biochem. Physiol. 35, 1165 (1957); E. Baer and D. Buchnea, Ibid. 37, 953 (1959); F. Kögl, G.H. de Haas and L.L.M. van Deenen, Rec. Trav. Chim. In press (1960).

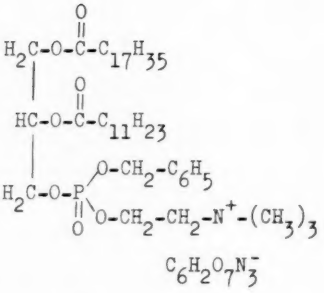
2 G.H. de Haas and L.L.M. van Deenen, To be published.



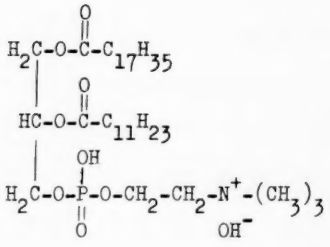
I



II



III



IV

γ-Octadecanoylglycerol[3] was converted with p-toluene-sulphonyl chloride in anhydrous pyridine into γ-octadecanoyl-α-(p-toluenesulphonyl)-glycerol, which upon treatment with sodium iodide in acetone provided γ-octadecanoyl-α-iodohydrin, as colourless crystals from methanol (yield 70%; m.p. 61.5°); (Found: C, 53.59; H, 8.80. $C_{21}H_{41}O_3J$ requires C, 53.84; H, 8.82). The melting point is identical with that of γ-octadecanoyl-α-iodohydrin prepared according to Wohl,[4] by acylating α-iodohydrin directly with octadecanoyl chloride.

This compound upon acylation with dodecanoyl chloride in anhydrous

---

[3] E. Baer and H.O.L. Fischer, J. Amer. Chem. Soc. 67, 2031 (1945).

[4] H. Wohl, Inaug.-Diss. Techn. Hochschule München (1927).

pyridine yielded γ-octadecanoyl-β-dodecanoyl-α-iodohydrin (I), as colourless crystals from methanol (yield 95%; m.p. 33.5°); (Found: C, 61.06; H, 9.90. $C_{33}H_{63}O_4J$ requires C, 60.94; H, 9.73).

By treatment with silver dibenzylphosphate, according to Hessel et al.,[5] I was converted in nearly quantitative yield into dibenzyl γ-octadecanoyl-β-dodecanoylglycerol phosphate; colourless crystals from methanol (m.p. 39°); (Found: C, 70.40; H, 9.82; P, 3.71. $C_{47}H_{77}O_8P$ requires C, 70.46; H, 9.69; P, 3.86).

Monodebenzylation of this dibenzylester with sodium iodide in acetone according to Gielkens et al.,[6] furnished the corresponding sodium salt (II), as a white powder (yield 90%);(Found: C, 65.38; H, 9.68; P, 4.20. $C_{40}H_{70}O_8PNa$ requires C, 65.55; H, 9.63; P, 4.23). This sodium salt was readily converted in a 90% yield into the corresponding silver salt; colourless crystals from acetone (m.p. 54°); (Found: C, 59.01; H, 8.26; P, 3.70. $C_{40}H_{70}O_8PAg$ requires C, 58.74; H, 8.63; P, 3.67).

The silver salt thus obtained, was allowed to react with 2-bromo-ethylene trimethylammonium picrate[7] (100% excess) by refluxing in tetrahydrofurane for 24 hr in the dark. After removal of the precipitated silver bromide and the excess 2-bromo-ethylene trimethylammonium picrate, the benzyl γ-octadecanoyl-β-dodecanoyl-glycerol-α-phosphorylcholinepicrate (III) was obtained as a waxy, yellow solid in a yield of 96%.

---

[5] L.W. Hessel, I.D. Morton, A.R. Todd and P.E. Verkade, Rec. Trav. Chim. 73, 150 (1954).

[6] J.W. Gielkens, M.A. Hoefnagel, L.J. Stegerhoek and P.E. Verkade, Rec. Trav. Chim. 77, 656 (1958).

[7] I. Kabashima, Ber. 71, 1073 (1938).

Decomposition of this picrate in acetone with Amberlite IR-45 yielded the corresponding free base. After removal of the benzyl group by hydrogenolysis in absolute ethanol, using a palladium-active carbon catalyst,[6] we obtained in a 96% yield the "mixed-acid" lecithin (IV), a colourless powder from ether with m.p. 211-212°.

The lecithin was analysed as cadmium chloride adduct (Found: C, 45.31; H, 7.76; N, 1.49; P, 3.02. $(C_{38}H_{78}O_9NP)_2(CdCl_2)_3$ requires: C, 45.68; H, 7.87; N, 1.40; P, 3.10).

Saponification of the free lecithin and analysis of the fatty acids by gas-liquid chromatography ascertained the presence of equimolar amounts of octadecanoic acid (recovered: 99%) and dodecanoic acid (recovered: 98%).

The foregoing procedure was also employed for the synthesis of the structural isomer γ-dodecanoyl-β-octadecanoyl-α-lecithin. Both isomers, and corresponding "mixed-acid" α-lecithins obtained by acylating lysolecithins, will be further characterized by physical and biochemical analysis. The synthesis of lecithins containing two identical acyl groups was also achieved, but in this case the described method appeared to be more elaborate than the preparation of these lecithins by the direct acylation of L-α-glycerylphosphorylcholine.[1] The lecithins obtained by both procedures proved to be identical, indicating once more the validity of the present method. The synthesis of optically pure "mixed-acid" L-α-lecithins and lecithins containing both a saturated and an unsaturated fatty acid, is in progress. Full details will be reported elsewhere.

The authors are indebted to Prof. G.J.M. van der Kerk for his kind interest, and also to Dr. I. Mulder for his gas-chromatographic analysis of fatty acids.

Tetrahedron Letters No. 9, pp. 5-11, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

THE SYSTEM LEWIS ACID - NITRO COMPOUND AS A STRONG ELECTRON ACCEPTOR[1]

H.M.Buck, W.Bloemhoff* and L.J.Oosterhoff

Department of Theoretical Organic Chemistry

University of Leyden, Holland

(Received 15 March 1960)

In a search for methods of preparing positive ions of aromatic molecules the strong electron affinity of nitro compounds in combination with acids was found.

A very pronounced electron attracting power is displayed by the system aluminium chloride-nitromethane. In a solution of 2% aluminium chloride in nitromethane anthracene is readily converted into the monovalent positive ion (anthracene minus one electron). The green-blue solution exhibits electron spin resonance (ESR) and the UV absorption spectrum is similar to that of the monovalent ion of anthracene (see e.g.[2]).

TetT 9/A+

---

*One of us (W.B.) gratefully acknowledges financial support by the Netherlands Organisation of Pure Research (Z.W.O.).

[1] H.M.Buck, Thesis Leyden chapter VI (1959).

[2] W.Y.Aalbersberg, G.J.Hoijtink, E.L.Mackor and W.P.Weijland, J.Chem.Soc. 3049 (1959).

W.Y.Aalbersberg, G.J.Hoijtink, E.L.Mackor and W.P.Weijland, J.Chem.Soc. 3055 (1959).

If 1,1,2,2-tetra(p-methoxyphenyl)ethene is dissolved in such a solution the formation of a divalent positive ion can be demonstrated by comparing the spectrum with that of the perchlorate in nitromethane (fig. 1). From the complete agreement of the two spectra it follows that the ethene has given up two electrons.

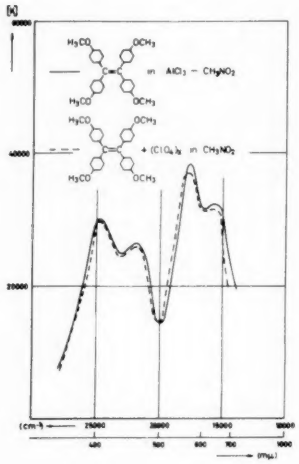


FIG. 1

Similarly 4,4'-dimethoxydiphenyl reacts with aluminium chloride-nitromethane under formation of the monovalent positive ion (fig. 2) *

*If the concentration of 4,4'-dimethoxydiphenyl is small the solution is red and the UV absorption is completely different from the monovalent positive ion. It may be of interest to note that this absorption band may be related to the small band at the same position in the spectrum of the irradiated solution of 4,4'-dimethoxydiphenyl in boric acid glass (fig. 2).

1960

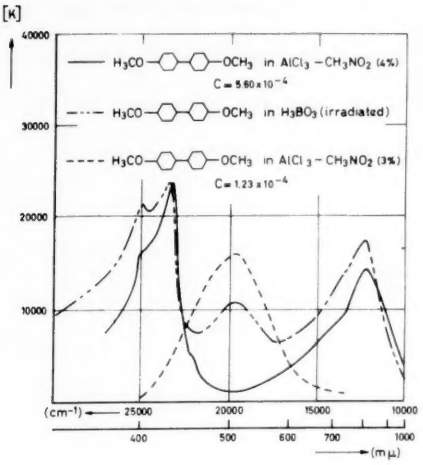


FIG. 2

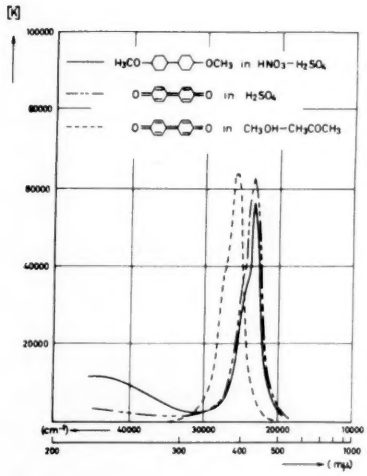


FIG. 3

This solution exhibits strong ESR. The same reaction occurs in a solution of aluminium chloride in nitrobenzene, although in general nitrobenzene-aluminium chloride is less active than nitromethane-aluminium chloride.

An even stronger electron abstracting power is displayed by the system nitric acid-sulphuric acid. This could be established by dissolving 4,4'-dimethoxydiphenyl in sulphuric acid containing a small amount of nitric acid or by dissolving the dark blue molecular compound 4,4'-dimethoxydiphenyl.2 HNO_3[3] in sulphuric acid.[4] The yellow solution contains the divalent positive ion as appears from the UV absorption spectrum (fig. 3).

It was also observed that the addition of a small amount of nitromethane to sulphuric acid gives rise to a solution with strong electron acceptor properties. Triphenylene in sulphuric acid is colourless but if some nitromethane is added the solution turns blue. This solution, however, exhibits no ESR. Triphenylene in aluminium chloride-nitromethane gives a paramagnetic solution and the UV absorption spectrum shows some similarity to that of the monovalent ion.[5]

With aromatic hydrocarbons having a low ionisation energy the activity of a solution of aluminium chloride in nitromethane may be

---

[3] J.van Alphen, Recueil 49, 771 (1930).

[4] H.M.Buck, Thesis Leyden chapter III (1959).

[5] P.Balk, G.J.Hoijtink and J.W.H.Schreurs, Recueil 76, 813 (1957).

1960

too high, leading to secondary reactions. With perylene the formation of the monovalent positive ion in aluminium chloride-nitrobenzene could easily be demonstrated. The UV spectrum characteristic of the monovalent positive ion[2] remains nearly unchanged for days. The solution in aluminium chloride-nitromethane, however, is very unstable and neither the monovalent positive ion nor the divalent positive ion could be found. If the activity of the solution was lowered by the addition of carbon tetrachloride the monovalent positive ion could be identified.

In all our experiments the formation of the monovalent positive ions was checked, if possible, by ESR measurements and by comparing the UV absorption spectra with known absorption spectra of the monovalent and divalent negative or positive ions.[5,6]

Apart from the acids and nitro compounds mentioned a large number of other acid-nitro compound systems have been studied with respect to various aromatic compounds. The results of these experiments together with results on the influence of temperature and irradiation will be published elsewhere.

In general it was found that most aromatic hydrocarbons dissolved in nitromethane, to which a small amount of aluminium chloride has been added, give coloured solutions. For instance benzene dissolves

---

[6] P.Bennema, G.J.Hoijtink, J.H.Lupinski, L.J.Oosterhoff, P.Selier and J.L.W.van Voorst, Mol.Phys. 2, 431 (1959)

with an orange colour, naphthalene gives a red solution. In neither solution could ESR be detected. The correlation between the ionisation energy of the aromatic molecule and the bathochromic shift of the colour of the solution suggests the formation of charge transfer complexes as was first pointed out by Wizinger.[7] The appearance of colour on the addition of benzene to a solution of aluminium chloride-nitromethane was also observed by Schmerling.[8] Similar observations have been made by H.C.Brown and Grayson[9] for a number of aromatic hydrocarbons with aluminium chloride-nitrobenzene. According to these authors it would appear that the aluminium chloride greatly increases the electrophilic character of the nitrobenzene molecule and brings about stable complex formation with aromatic hydrocarbons of high basicity. In view of our experiments it seems reasonable to assume that in general the combination acid-nitro compound must be considered as an electron acceptor.

In connection with the phenomena discussed in this paper it may be of interest to mention the characteristic colour of solutions of substituted benzenes and nitric acid in nitromethane which were observed by Ingold et al.[10] Our experiments suggest that these colours are to be ascribed to charge transfer complexes. The correlation

---

[7] R.Wizinger, Organische Farbstoffe 48-51 (1933).

[8] L.Schmerling, Ind.Eng.Chem. 40, 2072 (1948).

[9] H.C.Brown and M.Grayson, J.Amer.Chem.Soc. 75, 6285 (1953).

[10] G.A.Benford and C.K.Ingold, J.Chem.Soc. 929 (1938).

between colour and nitration velocity found by Ingold et al. suggests that the formation of a charge transfer complex may be an essential step in the nitration process (cf. R.D.Brown[11]).

---

[11] R.D.Brown, J.Chem.Soc. 2224 (1959).

1960

Tetrahedron Letters No. 9, pp. 12-13, 1960. Pergamon Press Ltd. Printed in Great Britain.

PHOTOCATALYSED CYCLISATION OF AZOBENZENE

G. E. Lewis

Organic Chemistry Department, University of Adelaide, South Australia

(Received 16 March 1960)

RECENTLY we have observed that azobenzene when exposed to light in solutions containing high concentrations of sulphuric acid, undergoes oxidative cyclization to 3,4-benzocinnoline. Although fusion of azobenzene with aluminium chloride[1] is known to yield 3,4-benzocinnoline, no report of a photocatalysed cyclization of this type has appeared.

Azobenzene (200 mg) was dissolved in a mixture of ethanol (50 cc) and 24 N sulphuric acid (150 cc) and the solution exposed to sunlight for 5 hr. A benzene extract of the neutralized solution was then passed through a column of alumina, elution of the product being effected with a mixture of chloroform (10% v:v) and benzene. After evaporation of the solvent and crystallization from aqueous ethanol, 3,4-benzocinnoline (83 mg), m.p. 154° was obtained. Its identity was established by mixed melting point determination with an authentic sample[2] and comparison of ultra-violet absorption spectra in neutral and acidic solutions.

Spectroscopic studies have revealed that several other aromatic azo-compounds behave in a similar manner. The general applicability of the

---

[1] A. Wolfram, E. Hausdorfer and L. Schornig, (Ger. Pat. 513, 206) Friedlander 17, 650 (1932).

[2] G.M. Badger, J.H. Seidler and B. Thompson, J.Chem.Soc. 3207 (1951).

reaction and its mechanism are being investigated and details will be published at a later date.

Azoxybenzene and 2-hydroxyazobenzene were found not to cyclize under these conditions and therefore the possibility of these compounds being intermediate in the transformation of azobenzene is precluded.

No significant difference could be detected between the rates of cyclization of cis- and trans-azobenzene and this was shown to be the result of cis $\rightleftharpoons$ trans equilibration proceeding at a much higher rate than cyclization.

Tetrahedron Letters No. 9, pp. 14-15, 1960. Pergamon Press Ltd. Printed in Great Britain.

A NEW REAGENT FOR THE SELECTIVE OXIDATION OF STEROIDAL ALLYLIC ALCOHOLS TO αβ-UNSATURATED KETONES

D. Burn, V. Petrow and G. O. Weston

Chemical Research Laboratories, The British Drug Houses Ltd.,

London N.1

(Received 11 March 1960; in revised form 23 March 1960)

IN a previous communication[1] we reported the conversion of steroidal 4-en- and 4,6-dien-3-ones into the corresponding 1,4-dien and 1,4,6-trien-3-ones by the use of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ).[2] We now find that DDQ selectively oxidizes steroidal allylic alcohols to the corresponding αβ-unsaturated ketones in excellent yield.* The reaction is conveniently performed at room temperature by adding a slight excess of DDQ dissolved in dry benzene or dioxan to a solution of the steroid in the same solvent. Precipitation of the hydroquinone begins almost immediately and the reaction is generally complete within 5 - 15 hr. Under these conditions 1,2-dehydrogenation[1] does not occur and saturated alcohols are completely unaffected.

---

* Braude et al.[3] have described the oxidation of cholest-4-en-3β-ol to the 3-one using chloranil; the yield is however lower than that obtained with DDQ.

1 D. Burn, D.N. Kirk and V. Petrow, Proc. Chem. Soc. 14 (1960).

2 E.A. Braude, A.G. Brook and R.P. Linstead, J. Chem. Soc. 3569 (1954).

3 E.A. Braude, R.P. Linstead and K.R. Wooldridge, J. Chem. Soc. 3070 (1956).

1960

In addition, none of the other functional groups commonly encountered in steroid chemistry appear to be attacked by the reagent under the above experimental conditions. The hydroquinone formed during the reaction may be recovered and re-oxidized to DDQ if desired. In terms of speed and reproducibility, this reagent appears to offer advantages over manganese dioxide which has hitherto been employed for this purpose.[4]

The following transformations give some indication of the scope of the reaction:-

Androst-4-ene-3β,17β-diol 17β-hydroxyandrost-4-en-3-one (70%)

Androsta-1,4-diene-3β,17β-diol 17β-hydroxyandrosta-1,4-dien-3-one (45%)

Androsta-4,6-diene-3β,17β-diol 17β-hydroxyandrosta-4,6-dien-3-one (70%)

Androsta-1,4,6-triene-3β,17β-diol 17β-hydroxyandrosta-1,4,6-trien-3-one (50%)

Pregna-5,16-diene-3β,20β-diol 3β-hydroxypregna-5,16-dien-20-one (75%)

Pregn-4-en-3β,20β-diol 20β-hydroxypregn-4-en-3-one (70%)

Pregn-4-ene-3β,11β,20β-triol 11β,20β-dihydroxypregn-4-en-3-one (70%)

Cholest-5-ene-3β,4β-diol Cholestane-3,4-dione (via 3β-hydroxycholest-5-en-4-one) (75%)

Cholest-4-ene-3β,6β-diol 6β-hydroxycholest-4-en-3-one (60%)

25D-Spirost-9(11)-ene-3β,12β-diol 3β-hydroxy-25D-spirost-9(11)-en-12-one (70%)

The presence of such substituents as methyl at C_2, C_4 and C_6 does not interfere with the oxidation of allylic-3-ols.

---

[4] F. Sondheimer and G. Rosenkranz, Experientia 9, 62 (1953).

Tetrahedron Letters No. 9, pp. 16-19, 1960. Pergamon Press Ltd. Printed in Great Britain.

LA SYNTHESE TOTALE DE L'ETHER METHYLIQUE DU NIMBIOL

[(±) METHOXY-6 METHYL-7 PODOCARPATRIENE - 5,7,13 (14)][1]

M. Fétizon et J. Delobelle

Ecole Polytechnique, 17 rue Descartes, Paris Vo

(Received 22 March 1960)

SENGUPTA et ses collaborateurs ont isolé de la fraction phénolique d'un extrait de feuilles et d'écorce de Melia azadirachta Linn, deux phénols : le sugiol (I), déjà rencontré à maintes reprises, et le nimbiol, pour lequel la structure II_a a été établie.[2]

Une synthèse totale du (±) méthoxy-6 méthyl-7 podocarpatriène - 5, 7, 13 (14) et la comparaison de son spectre infra-rouge avec celui de l'éther méthylique II_b confirme l'exactitude de la structure proposée.

Le 11a méthoxy-6 podocarpatriène IV, dont la synthèse totale a été réalisée[3,4] a été oxydé par l'acide chromique dans l'acide acétique en cétone VI, huileuse, purifiée par chromatographie.[4] λ_m : 226 mμ; log ε : 4.00 (alcool); λ_m : 227 mμ; log ε : 4.06.

---

[1] La nomenclature employée est celle de W. Klyne, J. Chem. Soc. 3072 (1953).

[2] P. Sengupta, S. Choudhury et H. Khastgir, Chem. & Ind. 861 (1958); Ibid. 1284 (1959).

[3] M.F. Ansell et B. Gadsby, J. Chem. Soc. 2994 (1959).

[4] M. Fétizon et J. Delobelle, C.R. Acad. Sci., Paris 246, 2774 (1958).

2 - 4 Dinitro phenylhydrazone : F : 220° - 221°; λ_m : 399 mμ; log ε : 4.40 ($CHCl_3$).

On peut obtenir des quantités importantes de VI d'une pureté satisfaisante, en oxydant le produit brut IV + V de cyclisation de l'alcool éthylénique III, selon la technique de Wenkert Dans ces conditions, l'isomère 11β (V) est transformé totalement en dicétone VII. L'isomère 11α (IV) fournit la cétone VI, qui est isolée par chromatographie sur alumine.

La cétone VI est chlorométhylée en 11α-méthoxy-6 chrométhyl-7 podocarpatriène VIII. F : 155° - 157°; λ_m : 232 mμ; log ε : 4.27 (alcool); λ_m : 279 mμ; log ε : 4.16. (Trouvé: C, 70.64; H, 8.10. Calculé pour $C_{19}H_{25}O_2Cl$: C, 71.13; H, 7.86.

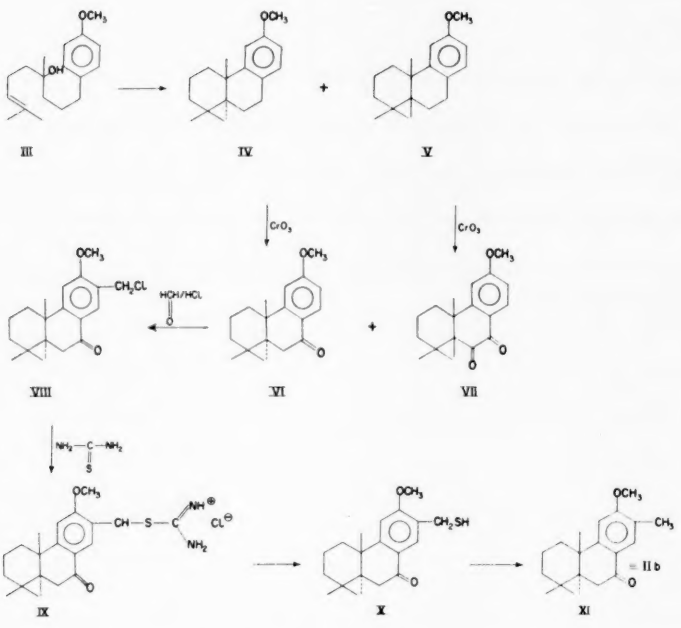
Le spectre infra-rouge de VIII comporte une bande à 866 cm^{-1} et aucune autre bande importante dans la région de 800 cm^{-1}, ce qui exclut l'existence de deux hydrogènes vicinaux sur le noyau aromatique.

La réduction de VIII par le zinc et l'acide acétique n'a pas donné de bons resultats.

La cétone VIII condensée avec la thiourée dans l'éthanol à reflux fournit le sel d'isothiouronium IX mal cristallise. Ce sel non purifié, traité sous azote par la soude aqueuse diluée (3 heures au bain-marie) conduit au mercaptan X. F : 121 - 123° (chromatographie et 3 cristallisations dans l'hexane). λ_m : 232.5 mμ; log ε : 4.15 (alcool); λ_m : 278.5 mμ; log ε : 4.04. (Trouvé: C, 71.40; H, 7.86. Calculé pour $C_{19}H_{26}O_2S$: C, 71.67; H, 8.23).

---

[5] E. Wenkert et B.G. Jackson, J. Amer. Chem. Soc. 80, 211 (1958).



Le mercaptan X est transformé en (±) 11α methoxy-6 methyl-7 podocarpatriène XI par chauffage à reflux dans l'éthanol avec un excès de nickel Raney.

A partir de 1.240 grammes de cétone VIII on a pu obtenir 490 mg de XI (chromatographie et 3 cristallisations dans le pentane). F : 108 - 110°. λ_m : 207 mμ; log ε : 4.13; λ_m : 232 mμ; log ε : 4.13; λ_m : 279 mμ; log ε : 4.11. (Trouvé: C, 79.87, H, 9.47. Calculé pour $C_{19}H_{26}O_2$: C, 79.68, H, 9.15).

Le spectre ultra-violet de XI est superposable à celui de l'éther méthylique du nimbiol II_b, pour lequel on a; F : 142 - 143°; α_D + 43°.7; λ_m : 207 mμ; log ε : 4.18 (alcool); λ_m : 232 mμ; log ε : 4.15; λ_m : 279 mμ; log ε : 4.12.

Les spectres infra-rouges (pastille dans K Br) de II_b et XI sont identiques.

Le nimbiol a donc bien la structure II_a

La cyclisation de l'alcool XII, et l'oxydation chromique du produit brut XIII n'ont pas donné XI. On n'isole qu'une très petite quantité de substance cristallisée qui n'a pu être identifiée avec certitude.

Nous remercions vivement le Dr. Sengupta pour un échantillon d'éther méthylique du nimbiol.

Tetrahedron Letters No. 9, pp. 20-23, 1960. Pergamon Press Ltd. Printed in Great Britain.

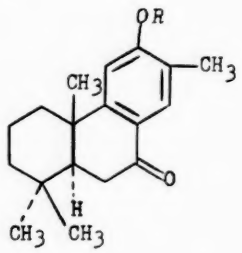
THE CONVERSION OF PODOCARPIC ACID TO NIMBIOL

Roy H. Bible, Jr.

Division of Chemical Research, G. D. Searle and Company
Box 5110, Chicago 80, Illinois

(Received 23 February 1960)

NIMBIOL[1], a compound isolated from the trunk bark of Melia azadirachta Linn., has been assigned[2-3] the structure Ia.



Ia. R=H

b. R=CH_3

We have converted podocarpic acid to compounds having structures Ia and Ib and have found them to be identical with nimbiol and nimbiol methyl ether[1] thus confirming the complete structures assigned[3] by Choudhuri, Khastgir and Sengupta.

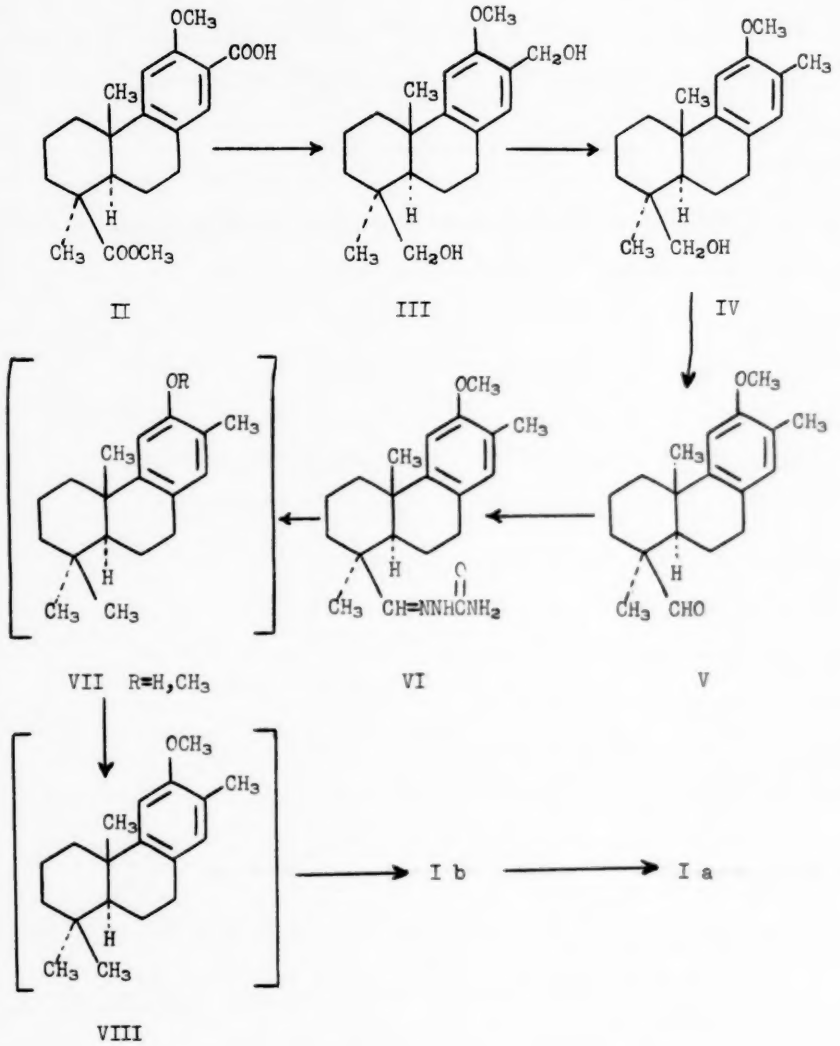
---

[1] P. Sengupta, S. N. Choudhuri and H. N. Khastgir, Chem. and Ind. 861 (1958).

[2] S. N. Choudhuri, H. N. Khastgir and P. Sengupta, Chem. and Ind. 634 (1959).

[3] S. N. Choudhuri, H. N. Khastgir and P. Sengupta, Chem. and Ind. 1284 (1959).

1960


OCH3
COOH
CH3
H
CH3 COOCH3
II
OCH3
CH2OH
CH3
H
CH3 CH2OH
III
OCH3
CH3
CH3
H
CH3 CH2OH
IV
OCH3
CH3
CH3
H
CH3 CHO
V
OCH3
CH3
CH3
H
CH3 CH=NNHCNH2
O
VI
OR
CH3
CH3
H
CH3 CH3
VII R=H,CH3
OCH3
CH3
CH3
H
CH3 CH3
VIII
I b
I a

Methyl O-methyl-7-carboxypodocarpate[4] (II) was reduced with lithium aluminum hydride in tetrahydrofuran to the glycol III; m.p. 119.5-122°; $[\alpha]_D$ +69°[5]; λ_{max}^{MeOH} 280 ($\log\epsilon$ = 3.46) and 285mμ ($\log\epsilon$ = 3.46). (Found: C,74.94; H, 9.19. $C_{19}H_{28}O_3$ requires: C, 74.96; H, 9.27%). Hydrogenolysis of III over palladium-charcoal in the presence of hydrochloric acid gave IV; m.p. 83-85°; $[\alpha]_D$ +68°; λ_{max}^{MeOH} 280 ($\log\epsilon$ = 3.47) and 287 mμ ($\log\epsilon$ = 3.47). (Found: C, 79.11; H, 9.94. $C_{19}H_{28}O_2$ requires: C, 79.12; H, 9.79). Oxidation of IV with chromic acid-sulfuric acid in acetone gave the aldehyde, V; m.p. 110-111.5°; $[\alpha]_D$ +87°; λ_{max}^{MeOH} 281 ($\log\epsilon$ = 3.49) and 286 mμ ($\log\epsilon$ = 3.48). (Found: C, 79.44; H, 9.31. $C_{19}H_{26}O_2$ requires: C, 79.68; H, 9.15). The aldehyde V was converted to the semicarbazone VI; m.p. 210-212°; λ_{max}^{MeOH} 280 ($\log\epsilon$ = 3.52) and 286mμ ($\log\epsilon$ = 3.49). (Found: C, 69.88; H, 8.38. $C_{20}H_{29}N_3O_2$ requires: C, 69.94; H, 8.51%). The semicarbazone (VI) was heated at 200° with sodium ethoxide in ethanol. The crude product (VII) was subjected to remethylation with dimethyl sulfate and sodium hydroxide followed by an oxidation with chromic acid in aqueous acetic acid to give Ib; m.p. 142-144°; $[\alpha]_D$ +43°; λ_{max}^{EtOH} 230 ($\log\epsilon$ = 4.16) and 277 mμ ($\log\epsilon$ = 4.12). This product was identical (no depression of the melting point on admixture; identical infrared absorption spectra at 5% in chloroform; identical ultraviolet spectra) with nimbiol methyl ether (reported[1]: m.p. 142-143°; $[\alpha]$ +43.7°). Demethylation of Ib with pyridine hydrochloride

---

[4] G. M. Picha, U. S. Patent 2,767,162 (1956).

[5] All rotations were determined using 1% solutions in chloroform.

gave the free phenol Ia; m.p. 248-252°; $[\alpha]_D$ +33°; λ_{max}^{EtOH} 234 (log ε = 4.13) and 283 mμ (log ε = 4.10); $\lambda_{max}^{0.1\ N\ NaOH/EtOH}$ 253 (log ε = 3.84) and 345 mμ (log ε = 4.38) [reported[1,2]: m.p. 244°; $[\alpha]_D$ +32.3°; λ_{max}^{EtOH} 231 (log ε = 4.07) and 286 mμ (log ε = 4.06); $\lambda_{max}^{0.1\ N\ NaOH/EtOH}$ 251 (log ε = 3.89) and 344 mμ (log ε = 4.33)]. Remethylation of this phenol (Ia) gave the original methyl ether (Ib).

We are highly indebted to Dr. P. Sengupta of the East India Pharmaceutical Works Ltd., Calcutta-34, India for the gift of the nimbiol methyl ether.

1960

Tetrahedron Letters No. 9, pp. 24-30, 1960. Pergamon Press Ltd. Printed in Great Britain.

ION PAIRS, NUCLEOPHILICITY AND SALT EFFECTS IN BIMOLECULAR NUCLEOPHILIC SUBSTITUTION[1]

S. Winstein, Lydia G. Savedoff,[2] S. Smith

I.D.R. Stevens and John S. Gall

Dept. of Chemistry, University of California, Los Angeles, Calif.

(Received 28 March 1960)

Second order rate constants for S_N2 reactions of lithium halides with alkyl halides and toluenesulfonates[3] in acetone correspond to an apparent nucleophilicity order, $I^- > Br^- > Cl^-$, in agreement with the one usually quoted.[4] It has been clear for some time, however, that the second order rate constants obtained under the usual kinetic conditions are far from actual rate constants for reaction of the organic substrates with dissociated halide ions. In this Communication we point out that the nucleophilicity order of the halides in acetone is actually $Cl^- > Br^- > I^-$, the exact reverse of that usually quoted.[4]

For bimolecular nucleophilic substitution reactions involving neutral

---

[1] Research supported by the National Science Foundation.

[2] National Science Foundation Science Faculty Fellow, 1959-1960.

[3] J. S. Gall, I.D.R. Stevens and S. Smith, unpublished work.

[4] e.g., (a) A. Streitwieser, Jr., Chem. Reviews 56, 571 (1956); (b) C. G. Swain and C. B. Scott, J. Am. Chem. Soc. 75, 141 (1953); (c) J. O. Edwards, ibid. 76, 1540 (1954), 78, 1819 (1956); (d) J. Hine, Physical Organic Chemistry. McGraw-Hill Book Co., New York, N. Y., 1956, p. 138; (e) E. S. Gould, Mechanism and Structure in Organic Chemistry. Henry Holt and Co., New York, N. Y., 1959, p. 258.

1960

substrates and anionic nucleophiles in acetone, second order rate constants tend to decrease with increasing concentration of the nucleophilic reagent. The University College, London, School has consistently ascribed this behavior to salt effects on the rate constant for the reaction.[5] The observation that the addition of lithium perchlorate decreases the second order rate constant in the reaction of lithium chloride with alkyl iodides[5c] was regarded as support for this interpretation. Moreover, in the reactions of lithium chloride[5c] and lithium bromide[5f] with alkyl iodides the rate constants were observed to decrease within a run. This was attributed to a negative salt effect due to a change in electrolyte composition during the reaction. This effect was associated with the negative salt effect order,[5f] LiI > LiBr > LiCl > LiF.

The observations of Ingold and coworkers[5] are more satisfactorily accounted for by taking account of ion association of the nucleophilic reagent and considering the relative reactivities of the dissociated anion,[6,7,8] ion pair,[6,7,8] ion triplet,[9] etc. Acree[6] very early ascribed

---

[5] (a) P.B.D. de la Mare, J. Chem. Soc. 3169 (1955); (b) E. D. Hughes, C. K. Ingold and J.D.H. Mackie, ibid. 3173 (1955); (c) E. D. Hughes, C. K. Ingold and J.D.H. Mackie, ibid. 3177 (1955); (d) P.B.D. de la Mare, ibid. 3180 (1955); (e) L. Fowden, E. D. Hughes and C. K. Ingold, ibid. 3187 (1955); (f) L. Fowden, E. D. Hughes and C. K. Ingold, ibid. 3193 (1955); (g) P.B.D. de la Mare, ibid. 3196 (1955); (h) P.B.D. de la Mare, L. Fowden, E. D. Hughes, C. K. Ingold and J.D.H. Mackie, ibid. 3200 (1955); (i) Y. Pocker, ibid. 3939 (1959).

[6] S. F. Acree, Am. Chem. J. 48, 353 (1912).

[7] A. Brändström, Arkiv Kemi. 11, 567 (1957).

[8] (a) C. C. Evans and S. Sugden, J. Chem. Soc. 270 (1949); (b) C. C. Evans and S. Sugden, J. Chim. Phys. 45, 147 (1948).

[9] R. D. Heyding and C. A. Winkler, Can. J. Chem. 29, 790 (1951).

downward trends in second order rate constants with increasing salt concentration to incomplete dissociation of the salt and the much greater reactivity of the dissociated anion compared to the ion pair. While the second order rate constant for the exchange reaction of lithium radio-bromide with n-butyl bromide in acetone at 25° varies by a factor of 3.6 over a 400 fold range of salt concentrations, Evans and Sugden[8] have shown that a steady value is obtained on the assumption that only dissociated bromide ion is reactive. Similar analyses have been employed by Swart and leRoux,[10] Olson,[11] Winkler,[9] Moelwyn-Hughes[12] and Lichtin.[13] In all of these cases, the reactivity of the dissociated ion was found to be much larger than that of the ion pair, although the exact contribution of the latter to the reaction rate is difficult to assess in some instances.

Since dissociated ions appear to be more reactive than ion pairs, the rate depression by lithium perchlorate observed by Ingold[5c] is to be ascribed to common ion repression of the dissociation of the lithium chloride rather than to a salt effect on the second order rate constant. Further, Ingold's[5f] empirical negative salt effect order is simply the order of decreasing ion pair dissociation constants in acetone (Table I), or in other words, the order of decreasing ability to repress the dissociation of the

---

[10] (a) E. R. Swart and L. J. leRoux, J. Chem. Soc. 2110 (1956); (b) L. J. leRoux and E. R. Swart, ibid. 1475 (1955).

[11] A. R. Olson, L. D. Frashier and F. J. Spieth, J. Phys. Chem. 55, 860 (1951).

[12] (a) E. A. Moelwyn-Hughes, Trans. Faraday Soc. 45, 167 (1949); (b) Farhat-Aziz and E. A. Moelwyn-Hughes, J. Chem. Soc. 2635 (1959).

[13] N. N. Lichtin and K. N. Rao, Abstracts, Division of Physical Chem. of the Am. Chem. Soc., Chicago, Illinois, Sept. 7-12 (1958) p. 12S.

1960

nucleophilic salt. This interpretation is supported by observations in these Laboratories on the effects of added common ion and non-common ion salts in bimolecular nucleophilic substitutions in acetone solvent. For example, the rate of reaction of isobutyl p-toluenesulfonate with 0.04 M lithium chloride in acetone at 50° is decreased by a factor of three when 0.02 M lithium perchlorate is added, but it is increased by a factor of two by added 0.02 M tetrabutylammonium perchlorate.

The importance of ion association in controlling apparent nucleophilicity becomes evident when reactivities of lithium and tetrabutylammonium halides are compared. For example, in the reaction of n-butyl p-bromobenzenesulfonate with 0.04 M halide salts in acetone at 25°, the reactivity pattern is the following:

$$\begin{array}{ccccc} \text{LiI, } 6.2 & > & \text{LiBr, } 5.7 & > & \text{LiCl, } 1.0 \\ \vee & & \wedge & & \wedge \\ (\text{n-Bu})_4\text{NI, } 3.7 & < & (\text{n-Bu})_4\text{NBr, } 18 & < & (\text{n-Bu})_4\text{NCl, } 68 \end{array}$$

With lithium halides the order, $I^- > Br^- > Cl^-$, is observed, while the reverse order obtains for the tetrabutylammonium salts. This reversal arises because tetra-n-butylammonium chloride reacts 68 times as fast as lithium chloride, while lithium iodide reacts more rapidly than tetra-n-butylammonium iodide by a factor of 1.7. Similar results have been obtained with isobutyl p-toluenesulfonate in acetone at 50.0°:

$$\begin{array}{ccccc} \text{LiI, } 10 & > & \text{LiBr, } 5.8 & > & \text{LiCl, } 1.0 \\ \vee & & \wedge & & \wedge \\ (\text{n-Bu})_4\text{NI, } 4.3 & < & (\text{n-Bu})_4\text{NBr, } 18 & < & (\text{n-Bu})_4\text{NCl, } 65 \end{array}$$

The present data suggest that the nucleophilicity order of anions in acetone is actually $Cl^- > Br^- > I^-$, the one observed with the more dissociated

tetrabutylammonium salts, and that the reactivity pattern of the lithium halides is governed largely by the extreme variation in the ion pair dissociation constants of the salts in acetone rather than by the inherent nucleophilicities of the anions.

While some contribution to the reaction rate in acetone may be made by species other than the dissociated halide ions, approximate second order rate constants, k_2, for reaction by way of dissociated anions may be estimated by dividing the apparent second order rate constant, k_2', by the degree of dissociation of the salt, α. The results of this treatment for n-butyl p-toluenesulfonate are summarized in Table I, the α values being obtained with the aid of measured values of the ion pair dissociation constants, K, and Debye-Hückel limiting law activity coefficients.

As is clear from Table I, the lithium and tetrabutylammonium salts lead to nearly the same k_2 values for the dissociated halide ions. These give the rate sequence, Cl^-, 18 > Br^-, 4 > I^-, 1.0. The Cl^- > Br^- rate sequence has also been observed with benzyl and 1-phenyl-2-propyl p-toluenesulfonates.[3] The Cl^- > Br^- > I^- order is also obtained with alkyl bromides as the substrates when the data of Ingold and coworkers[5b,d,e] are corrected for ion pairing. For example, with isopropyl bromide,[5b,d,e] the rate sequence becomes Cl^-, 11 > Br^-, 5 > I^-, 1.0 in acetone at 25°.

In general, the anion order in acetone is the reverse of that observed in water.[4] For example, for the reaction of methyl iodide with halide salts in water[10,14] at 25° the anion rate sequence is I^-, 160 > Br^-, 14 > Cl^-, 1.0. With methyl bromide in water[14] at 25°, the rate sequence is I^-, 140 > Cl^-, 1. Obviously, the change from water to acetone causes a reversal in

---

[14] (a) E. A. Moelwyn-Hughes, J. Chem. Soc. 779 (1938); (b) R. H. Bathgate and E. A. Moelwyn-Hughes, ibid. 2642 (1959).

TABLE 1. Summary of Rate Constants for the Reaction of n-Butyl p-bromobenzenesulfonate with 0.04 M Salts in Acetone at 25.0°

	Rate Constants, l. mole^{-1} sec.$^{-1}$			
Salt	10^4K	$10^3k_2'$	10^3k_2	Ave. 10^3k_2
$(n\text{-Bu})_4NCl$	22.8[15]	33.5	58	55
LiCl	0.027[16]	0.493	51	
$(n\text{-Bu})_4NBr$	32.9[17]	9.09	13	13
LiBr	5.22[8]	2.81	12	
$(n\text{-Bu})_4NI$	64.8[17]	1.68	2.0	3
LiI	69[16]	2.97	3.6	

the nucleophilicity order of the halides. The importance of the solvent is emphasized by the very large increases in rate associated with the solvent change from water to acetone. Even without recourse to specific solvation effects,[18] one could anticipate on electrostatic grounds[19] that solvent sensitivity of the halide ion reactions would increase in the order of decreasing anion size, namely, $I^- < Br^- < Cl^-$. This in turn makes a reversal in nucleophilicity order of the halides a perfectly logical result of a

---

[15] M. J. McDowell and C. A. Kraus, J. Am. Chem. Soc. 73, 3293 (1951).

[16] L. G. Savedoff, unpublished work.

[17] M. B. Reynolds and C. A. Kraus, J. Am. Chem. Soc. 70, 1709 (1948).

[18] e.g., (a) E.A.S. Cavell, J. Chem. Soc. 4217 (1958); (b) J. A. Leary and M. Kahn, J. Am. Chem. Soc. 81, 4173 (1959).

[19] e.g., (a) K. J. Laidler and H. Eyring, Ann. N. Y. Acad. Sci. 39, 303 (1940); (b) A. A. Frost and R. G. Pearson, Kinetics and Mechanism. John Wiley and Sons, Inc., New York, N. Y., 1953, pp. 135-138.

sufficiently large solvent change. The change from water to acetone increases k_2 by ca. 10^4 in the iodide ion-methyl iodide reaction.[20] However, the same solvent change is increasing k_2 for the chloride ion reactions by ca. 10^7.

The need to consider ion association in assessing nucleophilicity has a bearing on Bunnett's scrutiny of the dependence of relative nucleophilicities of the halide ions on the nature of the substrate (RCl, RBr, RI).[21] He employed the rate constants of Ingold and coworkers,[5] and these were variously affected by ion association, common ion repression and the method of calculation. For example, the rate constant for the reaction of lithium chloride (0.032 M) with alkyl iodides was considerably depressed by the presence of 0.11 M lithium perchlorate;[5c] however, when alkyl bromides were studied no lithium perchlorate was added.[5d] In the reaction of lithium bromide with alkyl iodides[5f] the rate constant was calculated by a procedure which gives a value which is inevitably too low. In addition, different salt concentrations were employed with the different alkyl halides. These factors influence the derived rate comparisons.

---

[20] E. R. Swart and L. J. leRoux, J. Chem. Soc. 406 (1957).

[21] J. F. Bunnett, J. Am. Chem. Soc. 79, 5969 (1957).

1960

196

Tetrahedron Letters No. 10, pp. 1-9, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

THE CONSTITUTION OF RING A IN ACONITINE

F. W. Bachelor, R. F. C. Brown and G. Büchi

Department of Chemistry, Massachusetts Institute of Technology

Cambridge, Massachusetts, U. S. A.

(Received 29 March 1960)

IN a collaborative paper we recently proposed structure I for the modified diterpene alkaloid aconitine.[1] The results of a complete X-ray analysis[2] of demethanolaconinone hydriodide trihydrate (II) are in agreement with our views and beyond that provide the absolute[3] and relative configurations of thirteen out of the fifteen asymmetric centers present in aconitine. We now wish to present findings concerning the location of the 1,3-glycol-monomethylether grouping in ring A, for which chemical evidence was lacking,[1] and the configurations of the two remaining asymmetric centers. It was previously argued on chemical grounds that aconitine could not possess a hydroxyl group at C_1 because no carbinolamine ether is formed on oxidation of the alkaloid with chromium trioxide[4] while such

TET 10/A

---

[1] K. Wiesner, M. Götz, D. L. Simmons, L. R. Fowler, F. W. Bachelor, R. F. C. Brown and G. Büchi, Tetrahedron Letters 2, 15 (1959).

[2] M. Przybylska and L. Marion, Can. J. Chem. 37, 1116 (1959).

[3] M. Przybylska and L. Marion, Can. J. Chem. 37, 1843 (1959).

[4] H. Mayer and L. Marion, Can. J. Chem. 37, 856 (1959).

products are obtained by oxidation of delcosine[5] and delsoline[6] with potassium permanganate or silver oxide. Such reasoning, unfortunately, is not acceptable because it is based on negative evidence and structures (V)[6] for the carbinolamine ethers which are geometrically impossible.

We felt that the location of the hydroxyl function in ring A could be ascertained most conveniently by lactone formation between it and a carboxyl group to be generated at C_4. The recently reported cleavage of the bisnitrone III to the dimer of 4-methyl-4-nitrosopentanoic acid (IV) by sodium periodate[7] suggested that oxidation of the nitrone VII, m.p. 210-212°; λ_{max}^{EtOH} 233 mμ, ε 18620; λ_{210} ε 5000; $\nu_{max}^{CHCl_3}$ 1720 (benzoate), 1605 cm^{-1} (nitrone); $[\alpha]_D^{27}$ +13° (c, 3.09 $CHCl_3$). [Calcd. for $C_{31}H_{41}O_{11}N$: C, 61.66; H, 6.85; N, 2.32; 5 OCH_3, 25.70%. Found: C, 61.41; H, 7.02; N, 2.21; OCH_3, 25.02%] may yield the desired hydroxyacid. The required intermediate VII was available from the pentacyclic nitrone (VI)[1] by treatment with methanolic perchloric acid followed by aerial oxidation of the intermediate hydroxylamine in the presence of cupric ion. In fact, oxidation of VII with hot aqueous periodic acid yielded a crystalline, neutral, blue colored compound (VIII) rather than a carboxylic acid, which had m.p. 233-234° (dec.); $\lambda_{max}^{acetone}$ 670 mμ, ε 23; λ_{max}^{EtOH} 230 mμ, ε 16000; ν_{max}^{Nujol} 1745 (γ-lactone), 1721 (benzoate), 1563 cm^{-1} (nitroso). Calcd. for $C_{30}H_{35}O_{12}N$: C, 59.89; H, 5.87; N, 2.33; 4 OCH_3, 20.61 ; 5 OCH_3, 25.76%. Found: C, 59.66; H, 5.97; N, 2.44; OCH_3, 20.63%. Oxidation of

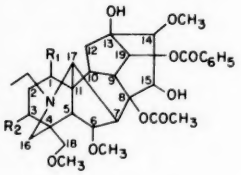
---

[5] R. Anet, D. W. Clayton and L. Marion, Can. J. Chem. 35, 397 (1957).

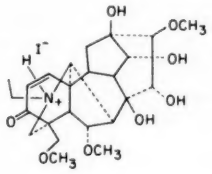
[6] F. Sparatore, R. Greenhalgh and L. Marion, Tetrahedron 4, 157 (1958).

[7] V. M. Clark, B. Sklarz and (Sir) Alexander Todd, J. Chem. Soc. 2123 (1959).

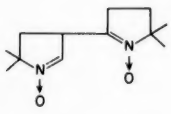
1960



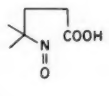
I $R_1 = OCH_3$; $R_2 = OH$
or $R_1 = OH$; $R_2 = OCH_3$



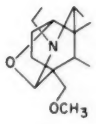
II



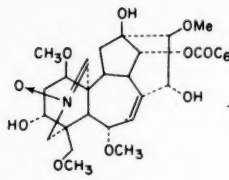
III



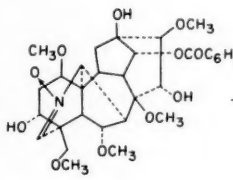
IV



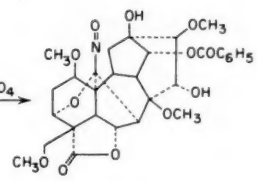
V



VI



VII



VIII

N-desethylpyroaconitine-Δ^{16}-nitrone[1] (IX) under identical conditions gave an analogous crystalline nitroso derivative (XI), m.p. 237-238° (dec.); $\lambda_{max}^{acetone}$ 685 mμ, ε 23; λ_{max}^{EtOH} 232 mμ, ε 13000; ν_{max}^{Nujol} 1750 (shifted to 1770 in $CHCl_3$)[8] (γ-lactone), 1720 (benzoate), 1705 (cyclohexanone), 1550 cm^{-1} (nitroso). Calcd. for $C_{29}H_{31}O_{11}N$: C, 61.15; H, 5.49; N, 2.46; 3 OCH_3, 16.35 ; 4 OCH_3, 21.80 ; act. H, 0.17%. Found: C, 60.78; H, 5.51; N, 2.34; OCH_3, 16.23 ; act. H, 0.12%. It was clear from the spectral data that a

---

[8] P. Wilder, Jr. and A. Winston, J. Am. Chem. Soc. 77, 5598 (1955). J. A. Berson, J. Am. Chem. Soc. 76, 4974 (1954).

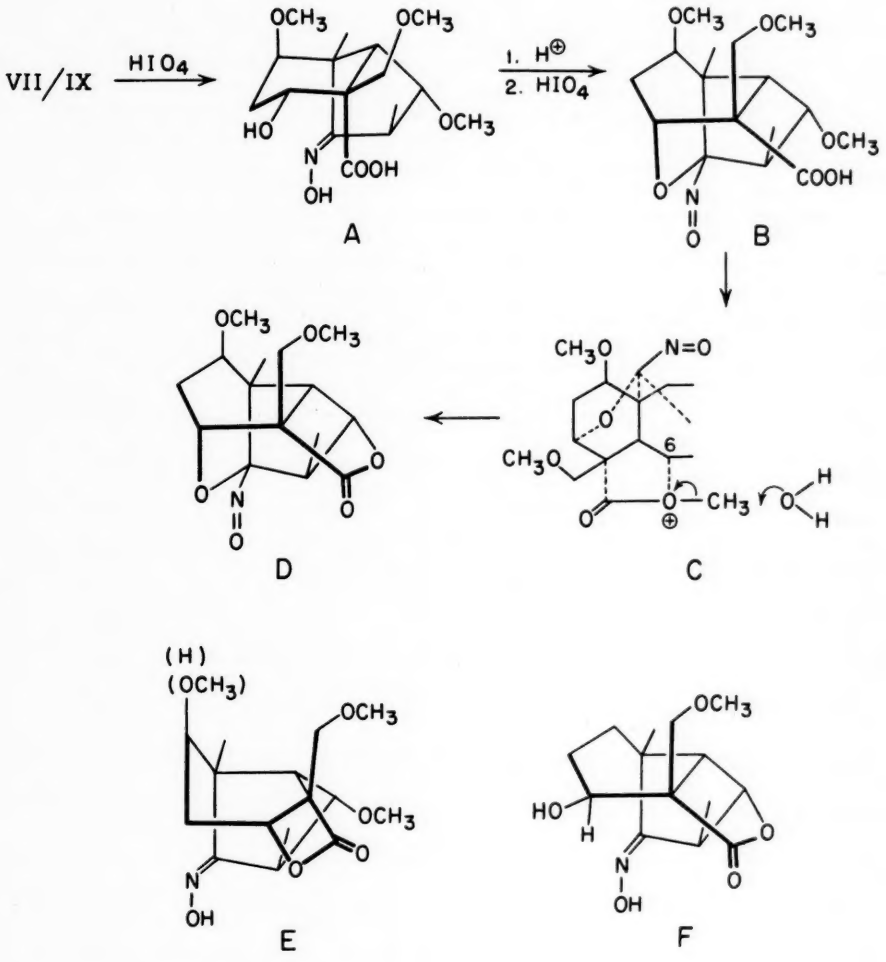
nitroso group and a γ-lactone ring were present in both substances. They furthermore contained one methoxyl group less than their precursors VII and IX and the second transformation also demonstrated that the methoxyl at C_8 was not involved. The formation of the nitroso derivatives can be rationalized by the sequence VII/IX ⟶ A ⟶ B ⟶ C ⟶ D. Non-bonded interactions between the carboxyl group and the oxime function as well as between the substituents at the peri-positions C_4 and C_6 operating in A are absent in D. Internal ether formation, indicated by the presence of nitroso derivatives rather than oximes and by the active hydrogen content of XI, is sterically only feasible if the hydroxyl group in ring A is at C_3 and α-oriented. Analogies for the postulated intermediate C have been provided[9] and the steric relationship of the carboxyl- and methoxyl-substituents in B is such that displacement must have occurred on the methyl group rather than on C_6. This unusually facile lactonization across the peri-positions provides chemical evidence for both location and orientation of the methoxyl function at C_6 and is, incidentally, analogous to the tetrahydrofuran ring formation across the same positions in delphinine.[10]

---

[9] D. S. Noyce and H. I. Weingarten, J. Am. Chem. Soc. 79, 3093 (1957); 79, 3098 (1957).

[10] K. Wiesner, F. Bickelhaupt, D. R. Babin and M. Götz, Tetrahedron Letters 3, 12 (1959); K. Wiesner, F. Bickelhaupt and D. R. Babin, Experientia 15, 93 (1959); W. A. Jacobs and S. W. Pelletier, J. Am. Chem. Soc. 76, 161 (1954).

1960


VII/IX
HIO4
OCH3
OCH3
HO
OCH3
N
OH
COOH
A
1. H⊕
2. HIO4
OCH3
OCH3
OCH3
COOH
O
N
O
B
CH3O
N=O
O
6
CH3O
O
CH3
O
H
H
C
OCH3
OCH3
O
O
N
O
O
D
(H)
(OCH3)
OCH3
OCH3
N
OH
O
O
E
OCH3
HO
H
N
OH
O
O
F

TET 10/A+

Spectral analysis of the products formed in the two periodic acid oxidations revealed the presence of small quantities of materials which we believe to be β-lactones ($\nu_{max}^{CHCl_3}$ 1825 cm^{-1}) although the products could not be isolated in pure form. We did, however, succeed in the preparation of a pure β-lactone in the 1-desmethoxypyroaconitine series. Reduction of dihydrodemethanolaconitinone[4] with sodium borohydride gave a crystalline product, m.p. 171-174°, $[\alpha]_D^{25}$ +19.5° (c, 0.95 $CHCl_3$). Although the physical constants are in fair agreement (lit.[4] m.p. 171-173°; $[\alpha]_D^{27}$ +24° ($CHCl_3$)) with those previously reported, our product was a mixture of C_3-epimeric alcohols because acetate pyrolysis at 210° yielded crystalline 1-desmethoxypyroaconitine (XIV), m.p. 131-132°; $[\alpha]_D^{25}$ -96° (c, 1.03 $CHCl_3$); $\nu_{max}^{CHCl_3}$ 1720 cm^{-1} (benzoate, cyclohexanone). Calcd. for $C_{31}H_{41}O_8N$: C, 67.00; H, 7.44; N, 2.52%. Found: C, 67.11; H, 7.32; N, 2.72% and an amorphous fraction containing 3-epi-1-desmethoxypyroaconitine (XV). Oxidation of XIV with peracetic acid in chloroform gave the amorphous N-oxide m.p. 172-178° (dec.) which, like our other N-oxides,[1] is probably a mixture of the two anticipated diastereomers. It was transformed further to the hydroxylamine by pyrolysis at 185° which in turn was oxidized with potassium ferricyanide in aqueous methanol containing sodium bicarbonate to the crystalline nitrone (X), m.p. 243-244°; $[\alpha]_D^{25}$ -109° (c, 1.05 $CHCl_3$); ν_{max}^{Nujol} 1715 (benzoate, cyclohexanone), 1585 cm^{-1} (nitrone). Calcd. for $C_{29}H_{35}O_9N$: C, 64.31; H, 6.51; N, 2.59%. Found: C, 64.00; H, 6.53; N, 2.76%. An identical sequence of reactions performed on XV gave an isomeric, crystalline nitrone (XVI), m.p. 231-232°, $[\alpha]_D^{25}$ -191° (c, 0.21 $CHCl_3$); ν_{max}^{Nujol} 1708 (benzoate, cyclohexanone), 1600 cm^{-1} (nitrone). Calcd. for $C_{29}H_{35}O_9N$: C, 64.31; H, 6.51; N, 2.59%. Found: C, 63.98; H, 6.61; N, 2.65%. Further, we found that oxidation of X

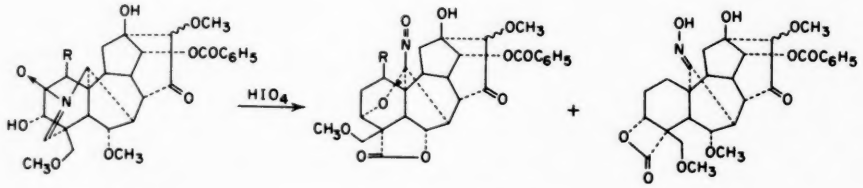
with hot aqueous periodic acid yielded two crystalline products separable by chromatography on acid-washed alumina. The less strongly adsorbed product was the blue nitrosolactone XII, m.p. 179-180° (from acetone-water); ν_{max}^{KBr} 1755 (1775 in $CHCl_3$) (γ-lactone), 1712 (benzoate, cyclohexanone), 1550 cm^{-1} (nitroso). Calcd. for $C_{28}H_{29}O_{10}N \cdot H_2O$: C, 60.32; H, 5.60; N, 2.51; 2 OCH_3, 11.13; 3 OCH_3, 17.22%. Found: C, 60.69; H, 5.61; N, 2.38; OCH_3, 11.27%. A striking property of the second product, m.p. 235-236° (dec. with gas evolution) [Calcd. for $C_{29}H_{33}O_{10}N$: C, 62.69; H, 5.99; N, 2.52; 2 OCH_3, 11.19; 3 OCH_3, 16.76%. Found: C, 62.57; H, 6.16; N, 2.40; OCH_3, 16.24%] was its infrared spectrum which exhibited bands in Nujol and chloroform at 1820 (β-lactone), 1710, 1695 cm^{-1} (benzoate, cyclohexanone, oxime) which we feel is in agreement with structure XIII. Not surprisingly the C=N vibration occurs at a high frequency and as the C=O vibration in cyclic ketones it is greatly affected by ring strain as exemplified by the following measurements in Nujol: cyclohexanoneoxime, 1662;[11] XVIII, 1680; XIX (prepared from bicyclo-[3,2,1]-octan-8-one[12]), 1690 cm^{-1}. These transformations provide further proof for the presence of a 3α-OH group in aconitine. As anticipated the oxidation of XVI with periodic acid yielded neither a β-lactone nor a nitroso-γ-lactone but a crystalline oximino-γ-lactone (XVII), m.p. 244-246° (from $CHCl_3$); $[\alpha]_D^{25}$ -150° (c, 0.23 $CHCl_3$); ν_{max}^{Nujol} 1755 (shifted to 1765 in $CHCl_3$)[8] (γ-lactone), 1710-1700 cm^{-1} (benzoate, cyclohexanone, oxime).

---

[11] A. Palm and H. Werbin, Can. J. Chem. 31, 1004 (1953).

[12] R. Mayer, G. Wenschuk and W. Töpelmann, Chem. Ber. 91, 1616 (1958); A. C. Cope, J. M. Grisar and P. E. Peterson, J. Am. Chem. Soc. in press, to whom we are indebted for a sample.

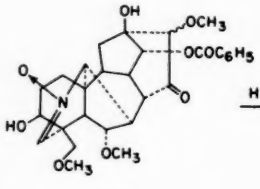
Calcd. for $C_{28}H_{31}O_{10}N \cdot CHCl_3$: C, 52.69; H, 4.88; N, 2.12; Cl, 16.10; 2 OCH_3, 9.39; 3 OCH_3, 14.09%. Found: C, 52.49; 52.47; H, 4.57; 4.67; N, 2.07; 1.96; Cl, 15.68; OCH_3, 9.19%. To secure further evidence for the presence of oxime functions in XIII and XVII, the compounds were heated with benzoyl peroxide and the resulting nitrous acid detected by



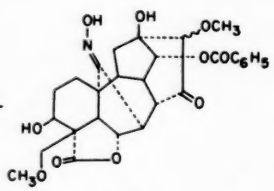
IX R = OCH_3
X R = H

XI R = OCH_3
XII R = H

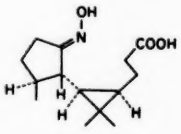
XIII



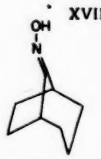
XVI



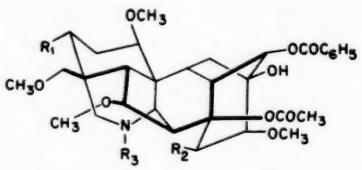
XVII



XVIII



XIX



XX R_1 = OH ; R_2 = OH ; R_3 = C_2H_5
XXI R_1 = H ; R_2 = H ; R_3 = CH_3

the sensitive Griess reagent.[13] Ring A in the oximino-γ-lactone (XVII) again must assume the boat form with equatorially disposed hydroxyl group to allow the formation of a strain free γ-lactone ring (cf. F). We have already pointed out that oxidative cleavage of the two nitrones VII and IX yields only minor quantities of β-lactones while approximately equal amounts of the β-lactone XIII and the γ-lactone XII are formed by oxidation of the desmethoxynitrone X under identical conditions. Consequently, the methoxyl group at C_1 seems to oppose β-lactone formation. If it is assumed that the fused β-lactone ring forces ring A into a pseudo-chair conformation the bulky methoxymethyl substituent at C_4 is quasi-axial and will destabilize a β-lactone by non-bonded interaction with the methoxyl group at C_1 if it is indeed axially oriented (cf. E). This argument is only suggestive and our proposal therefore tentative. Aconitine and delphinine have recently been correlated by Wiesner[14] and the two alkaloids are therefore represented by the complete structures XX and XXI.

We are much indebted to Chas. Pfizer and Co., Inc. for financial support and to the Alfred P. Sloan Foundation for a foreign postdoctoral fellowship to R. F. C. B.

1960

TET 10/6

---

[13] F. Feigl, Spot Tests in Organic Chemistry (5th edition), Elsevier, New York, N. Y. (1956), p. 228.

[14] K. Wiesner, D. L. Simmons and L. R. Fowler, Tetrahedron Letters 18, 1 (1959).

Tetrahedron Letters No. 10, pp. 10-18, 1960. Pergamon Press Ltd. Printed in Great Britain.

ECHITAMINE

(Mrs.) D. Chakravarti, R. N. Chakravarti, (Miss) R. Ghose

School of Tropical Medicine, Calcutta

and

Sir Robert Robinson

(Received 7 April 1960)

THE constituents of Alstonia scholaris have been investigated by the present Indian authors[1] since 1955 and with special reference to the main alkaloidal constituent, namely echitamine chloride.

The results, anticipated in part by other workers, will be published later in detail and the present communication, the outcome of our discussions, has become necessary in view of papers contributed by three groups of investigators.[2,3,4] These concur in attributing an eserine-like constitution to the alkaloid, mainly on spectrographic evidence. The hypsochromic shift of the U.V. absorption on the addition of acid[5] is held to be characteristic of the part structure Ar - N · C - N : . We do not regard this argument as conclusive.
(a) (b)

[1] Cf. R. Ghose, Ph.D. thesis, Calcutta University, 1957. Experimental results cited in the present memoir are due to the three first-named authors.

[2] T. R. Govindachari and S. Rajappa, Proc. Chem. Soc. 134 (1959).

[3] A. J. Birch, H. F. Hodson and G. F. Smith, Proc. Chem. Soc. 224 (1959)

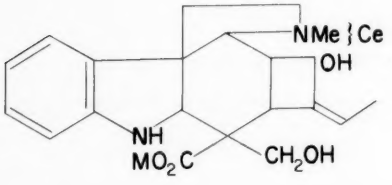
[4] A. Chatterjee, S. Ghosal and S. G. Majumdar, Chemistry and Industry 265 (1960).

[5] Hodson and Smith, J. Chem. Soc. 1877 (1957).

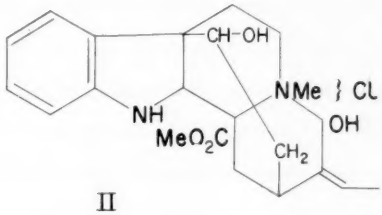
1960

The absorption is obviously due to the Ar N(a) conjugated system which can be modified by salt formation. The basic function of N(a) is in its turn influenced by the cationic charge on N(b) but it is a non sequitur to assume that this can only be effective in the group N(a) . C - N(b). Analogies from the chemistry of ajmaline[6] (III) akuammicine (IV) and pseudoakuammigine (V) combined with biogenetic considerations suggest the structures I or II for echitamine hydrochloride which serve to illustrate most of the chemistry of the alkaloid almost equally well.

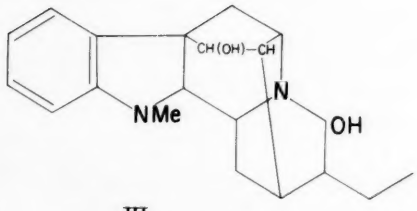
On balance I is favoured since it provides, as shown below, an easier explanation of the formation of a degradation product obtained on distillation over zinc dust (Birch et al, loc. cit.).



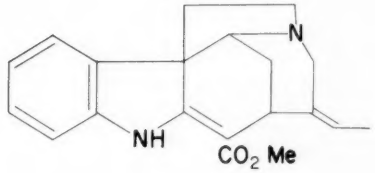
I



II

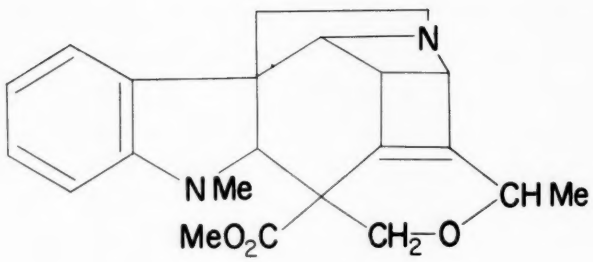


III



IV

[6] F.A.L. Anet, (Mrs.) D. Chakravarti, R. Robinson and E. Schlittler, J. Chem. Soc. 1242 (1954); F. C. Finch, J. D. Hobson, R. Robinson and E. Schlittler, Chemistry and Industry 653 (1955); R. Robinson Festschrift Arthur Stoll, Sandoz A.G., Basel, p. 457 (1957).



V

The composition of echitamine chloride, $C_{22}H_{29}O_4N_2Cl$ (including CO_2Me and (Me)N) indicates an α - or β -indole alkaloidal skeleton with C_{19} (C_{10} + C_8 + C, the so-called berberine bridge carbon atom).

The biogenesis of II can be contemplated along the usual lines for indole alkaloids in cases involving a Woodward fission. The carbomethoxy group is here in the position of the terminal carboxyl of the hypothetical hydroxylated phenylalanine precursor. On the other hand this confers no advantage over I, because the carbomethoxy group in the β -indole alkaloid structure is in precisely the same relative position with respect to the presumed amino-acid precursor as it occurs in yohimbine or corynantheine which belong to this α-indole alkaloid type. Hence the biogenetic arguments cancel, but whichever structure we take, an interesting biogenetic origin of the ester group is revealed.

The comparison of I and II is developed further below, but we now turn to the features common to the two structures. The ethylidene group is established by ozonisation of echitamine with formation of acetaldehyde. Birch, Hodson and Smith[3] extended a device that had been used in the ajmaline group (cf. Stoll Festschrift[6]) and showed

1960

that a catalytically reduced echitamine could be oxidised in a modified Kuhn-Roth process to a mixture of acetic and α -methylbutyric acids. We have found that echitamine is converted by hot 16% hydrochloric acid into the hydrochloride, m.p. 250-252°, of a t-base termed iso-echitamine. This affords formaldehyde instead of acetaldehyde on ozonisation. The explanation of the change is not clear. The colour reactions and reducing properties are also modified and something more profound than the simple shift of a bond -

$$\text{>C} = \text{CH} - \text{CH}_3 \longrightarrow \text{>CH} - \text{CH} = \text{CH}_2$$

has probably occurred. The liberation of an aldehyde function is also involved. The formation of dimethylechitamine by facile hydrolysis of echitamine, and its betaine-like character, has been recognised since the early work of Goodson[7] as evidence of a $\cdot CO_2Me$ group.

A diacetyl derivative affords evidence of :NH(a) and a hydroxyl group. The substance was prepared by the action of acetic anhydride on a pyridine solution of echitamine chloride at 100°. It crystallized from methanol-ether, m.p. 252°, $[\alpha]_D^{19}$ - 49.65. The analyses showed 2 Ac and agreed somewhat better with an anhydro-diacetyl derivative but the substance can be hydrolysed with regeneration of echitamine. The postulation of :N(a)Ac in this substance is based on the change of the colour reaction with nitric acid from red (echitamine) to violet and also by the change in U.V. absorption which resembles that between deacetylspermostrychnine (corresponding to echitamine) and spermostrychnine[8] (corresponding to diacetylechitamine). It appears therefore that echitamine contains only one hydroxyl group that can be acetylated under the conditions employed.

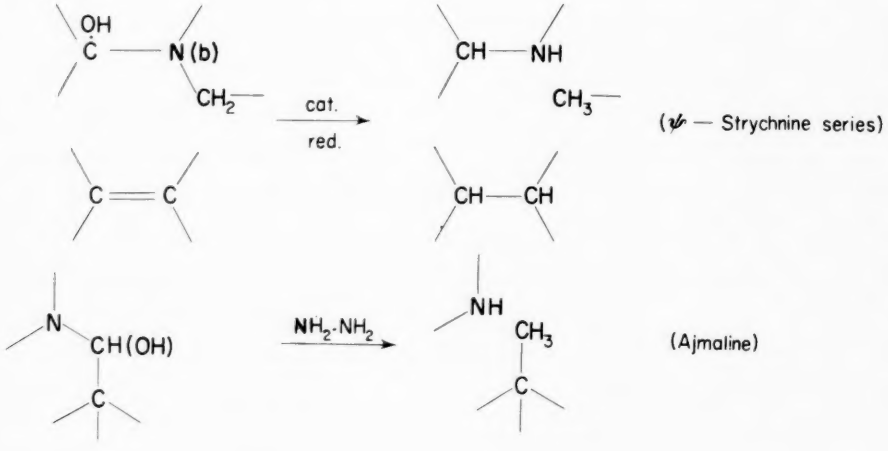
TET 10/8+

[7] J. M. Goodson and T. Henry, J. Chem. Soc. 127, 1640 (1925); Goodson, ibid. 2626 (1932).

[8] F.A.L. Anet and R. Robinson, J. Chem. Soc. 2253 (1955).

The catalytic hydrogenation of echitamine has been studied under various conditions. It was found that hydrogenolysis occurred, with or without saturation of the double bond. Hydrogenation of echitamine hydrochloride with Adams' PtO_2 catalyst in acetic acid medium gives a mixture of products from which deoxydihydro-echitamine, $C_{22}H_{30}O_3N_2$, m.p. 158-160° after shrinking at 130°, has been isolated.

In methanol the main product was a t-base, $C_{22}H_{28}O_3N_2$, which collapsed at 160° to an opaque mass clearing at 183-186°. This latter base furnished acetaldehyde on ozonolysis. The processes recalled the course of reduction of certain pseudo-strychnine and ajmaline derivatives in which we observe the changes:-



As in some of these cases (e.g. ajmaline) the hydrogenolysis results in formation of a new :CMe group. Deoxydihydro-echitamine is a t-base which does not give a red colouration with nitric acid. The simplest explanation of this curious property is that the ring fission has released strain and brought the $-CO_2Me$ group into closer relation

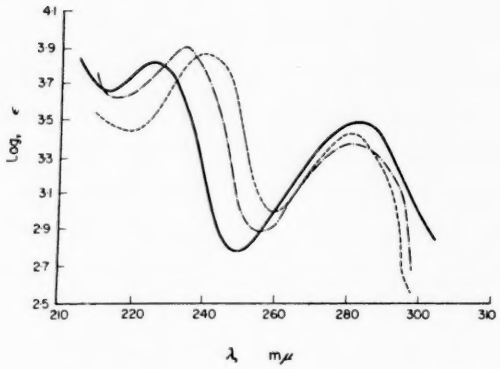
with N(a). Pseudo-akuammigine is doubtless a dihydro-indole and its failure to exhibit oxidation colour reactions can only be due to such association, a point which has already been made.[9]

Chatterjee et al[4] recognise the :N·C(OH):group but consider that the nitrogen concerned is N(a). This hypothesis is untenable because N(b) must in any case be quaternary and hence must suffer Emde reduction. Thus the N(a) CHOH theory requires fission at N(b) and deoxidation in the group attached to N(a). Thus all the relevant analogies are set aside. In addition we have adduced evidence that N(a) occurs as :NH, which can be acetylated and recovered on hydrolysis.

Furthermore the pka of echitamine hydrochloride is 9·1 which is the value noted for methylajmaline hydrochloride. This shows that methylajmaline and echitamine are notably stronger than ordinary t-bases, similar in structure, and also weaker than quaternary salts with usual reduced alkyl-type substituents. This special intermediate strength of the bases is evidently characteristic and is attributed to the group $\rangle\overset{+}{N}Me$ - CH(6H) -. Fission to $\rangle NMe$ O:CH· is not facile; there is pseudo-quaternary character; but it occurs at a lower pH than the Hofmann elimination, which of course may not occur at any pH. These facts find no explanation on the suggestion of Chatterjee et al. These authors state that the U.V. absorption spectrum of echitamine is that of an indoline base of eserine type. Actually it closely resembles the spectrum of various dihydroindole alkaloids as may be seen from the annexed comparison with pseudo-akuammigine and ajmaline.

---

9 R. Robinson and A. F. Thomas, J. Chem. Soc. 3479 and 3522 (1954)



Echitamine hydrochloride _____

Pseudo-akuammigine .-.-.-.-.-.-.-

Ajmaline ----------

In view of this conclusion the failure or reluctance of some colour reactions of echitamine and its derivatives (oxidation reaction with ferric chloride; coupling with diazobenzenesulphonic acid) poses the same problem as did pseudo-akuammigine. The only structural factor which provides some resource in this matter is the CO_2Me group, the position of which may facilitate a sufficient neutralisation of N(a). The structure of pseudo-akuammigine was formulated with this requirement in view. But in the case of the congeneric akuammicine the same position of the CO_2Me was indicated on quite independent grounds, namely that the base clearly contained the group

$$Ar\dot{N}(a)\cdot\dot{C}=\dot{C}-CO_2Me.$$

Karrer et al (loc. cit.) formulate a hydrogen bond between $\rangle$NH(a) and oxygen of carbonyl; we are not clear that this should supply the observed neutralisation of N(a).

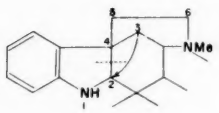
The suggested constitution of akuammicine[10] has now been confirmed

[10] K. Aghoramurthy and R. Robinson, Tetrahedron I, 172 (1957).

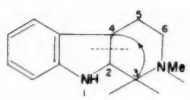
1960

by Professor P. Karrer (private communication) in that a Nb-methyl-akuammicine salt and flavocurarine[11] yield a salt of one and the same base on hydrolysis by elimination of CO_2Me and CHO, respectively. Thus the position selected for the $-CO_2Me$ group in I and II has been found to be correct for another indole alkaloid.

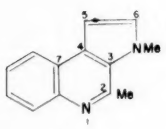
Finally, we note the structural changes required to derive 1'-methyl-pyrrolo (2':3'-3:4) quinoline (VI) from I and II. Actually it was a reduced t-base (hydrogenolysis and Emde reduction, but double bond intact) which was used by Birch, Hodson and Smith (loc. cit.). The same or a closely similar base had also been obtained in a similar manner by Govindachari and Rajappa (loc. cit.). Birch et al synthesised the substance.



Part of I



Part of II



VI

TET 10/6

In both cases the αβ position in the indole nucleus suffers fission. It will be seen that I does leave a carbon atom attached to position 2, even though it be a heavily substituted one. On the other hand, II provides no such source of the 2-methyl group of VI which would need to be introduced by migration.

[11] W. von Philipsborn, K. Bernauer, H. Schmidt and P. Karrer, Helv. Chim. Acta. XLII, 461 (1959).

After this note had been prepared for publication we read the communication of Conroy et al[12] on this topic and, as will be seen from the foregoing, find ourselves in agreement with most of the conclusions of these authors.

However, we greatly prefer the formula we have proposed on the methylajmaline model to that which the American workers adopt on the methyl-ψ-strychnine model.

In the first place it is not our experience that N(b) methyl-ψ-strychninum salts are so strongly quaternary as is echitamine. The former salts yield the keto-bases with weak alkalis.

An even more cogent argument is provided by the powerful reducing properties of echitamine base and of iso-echitamine. The latter base reduces ammoniacal silver solutions and Fehling's solution with great ease and echitamine itself exhibits the same property somewhat less readily. In this respect they resemble N(b) methylajmaline and oxo-dihydro-allostrychnine.[13] The ψ-strychnines do not exhibit strong reducing properties (cf. their preparation by means of oxidation[14]) which are evidently due to the aldehyde group liberated in alkaline solution from echitamine and ajmaline derivatives.

The formula I was foreshadowed in the Ph.D. (Calcutta) thesis of one of us[1] and it should also be pointed out that the akuammicine structure was clearly indicated[10] in 1957.

---

12 H. Conroy, R. Bernasconi, P.R. Brook, R. Ikan, R. Kurtz and K.W. Robinson, Tetrahedron Letters No. 6, 1 (1960).

13 R.N. Chakravarti, K.H. Pausacker and R. Robinson, J. Chem. Soc. 1555 (1947), cf.

14 A.S. Bailey and R. Robinson, J. Chem. Soc. 703 (1948). Cf. Nature Lond. 160, 18 (1947).

Dr. G.F. Smith (private communication) has informed us that he has been able to relate akuammicine to the Wieland-Gumlich aldehyde by conversion into one and the same substance, without loss of carbon, thus affording an elegant constitutional proof.

Tetrahedron Letters No. 10, pp. 19-25, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

THE STRUCTURES OF α- AND β-OBSCURINE

W. A. Ayer and G. G. Iverach

Department of Chemistry, University of Alberta.
Edmonton, Canada.

(Received 21 March 1960)

OBSCURINE, a minor alkaloid occurring in several species of Lycopodium, including L. obscurum L. var. dendroideum, was first isolated in 1942 by Manske and Marion[1]. Later[2], it was shown that obscurine is actually a mixture of two bases, α-obscurine ($C_{17}H_{26}ON_2$) and β-obscurine ($C_{17}H_{24}ON_2$). We now wish to report evidence which allows us to propose complete structures for these two alkaloids. Analytical results have confirmed the molecular formulas and have shown that, contrary to a previous report[2], both α- and

---

[1] R. H. F. Manske and L. Marion, Canad. J. Research B. 20, 87 (1942).

[2] B. P. Moore and L. Marion, Canad. J. Chem. 31, 952 (1953).

β-obscurine have an N-methyl group. Calc. for $C_{17}H_{26}ON_2$ (α-obscurine): C, 74.41; H, 9.55; N, 10.21; 1N-CH_3, 5.48; 1C-CH_3, 5.48%. Found: C, 74.43; H, 9.51; N, 10.27; N-CH_3, 5.49; C-CH_3, 3.03%. Calc. for $C_{17}H_{24}ON_2$ (β-obscurine): C, 74.96; H, 8.88; N, 10.29; 1N-CH_3, 5.52%. Found: C, 74.88; H, 8.74; N, 10.13; N-CH_3, 5.21, 5.42%.

Initial structural studies[2] on β-obscurine established the presence of an α-pyridone ring in the alkaloid and later work[3] indicated that the basic nitrogen is tertiary.

α-Obscurine does not exhibit the spectral properties of an α-pyridone, but shows instead a maximum in the ultraviolet at 255 mμ (log ε, 3.75)[2] and bands in the infrared (measured in CCl_4 solution) at 1675 cm^{-1} (strong, amide C=O) and 1700 cm^{-1} (medium intensity, C=C). However palladium-charcoal dehydrogenation of α-obscurine yields 6-methyl-α-pyridone[2], suggesting the presence of a partially reduced α-pyridone ring in the alkaloid. Attempted acetylation of α-obscurine with refluxing acetic anhydride-pyridine yielded starting material as the only isolable product, confirming the tertiary nature of the

---

[3] F. A. L. Anet and C. R. Eves, Canad. J. Chem. 36, 902 (1958).

basic nitrogen. Since both α- and β-obscurine show an N-H stretching band in the infrared, the non-basic nitrogen must be secondary.

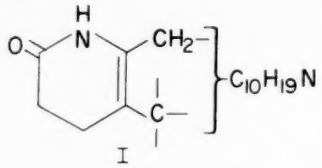
The possibility that α-obscurine contains a 5,6-dihydro-α-pyridone ring is ruled out by the spectral data already presented. The ultraviolet spectrum does not agree well with that of 6-methyl-5,6-dihydro-α-pyridone ($\lambda_{max.}$ 241, log ϵ 3.17)[4] and the high infrared frequency of the C=C stretching vibration suggests that the double bond is not conjugated to the carbonyl group but, by analogy with the structurally similar enol δ-lactones[5], is attached directly to the amide nitrogen. The nuclear magnetic resonance spectrum of α-obscurine shows that it carries no vinylic hydrogens, whereas that of β-obscurine shows two doublets (each corresponding to one hydrogen) in the double-bond region. The formation of 6-methyl-α-pyridone on dehydrogenation, together with other data outlined above and the fact that α-obscurine contains only one C-methyl group (Kuhn-Roth determination) present in the grouping $\geq CHCH_3$ (NMR), may be interpreted in terms of partial structures I and II for α- and β-obscurine,

---

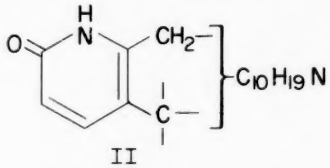
[4] O. E. Edwards and T. Singh, Canad. J. Chem. 32, 683 (1954).

[5] R. N. Jones and B. S. Gallagher, J. Amer. Chem. Soc. 81, 5242 (1959).

respectively.



I



II

It was now necessary to prove unambiguously that α-obscurine is simply dihydro-β-obscurine.

Attempts to selectively remove two hydrogen atoms from α-obscurine by hydrogen exchange with chloranil were unsuccessful. However, treatment of α-obscurine with N-bromosuccinimide in refluxing carbon tetrachloride containing a trace of benzoyl peroxide, followed by chromatography of the basic products over alumina, gave, in about 30% yield, β-obscurine (m.p. 316° (dec.), m.m.p. undepressed). The infrared and ultraviolet spectra were identical with those of an authentic sample. Inspection of the ultraviolet spectrum of the crude products indicated that dehydrobromination had occurred prior to chromatography.

Palladium dehydrogenation of α-obscurine gives, besides 6-methyl-α-pyridone, 7-methylquinoline[2]. Assuming that no rearrangement of the carbon skeleton has occurred during the dehydrogenation, and that the tertiary N-methyl must be eliminated to allow aromatization of the

quinoline ring, these fragments account for all the carbon, nitrogen and oxygen atoms of α-obscurine.

The Lycopodium alkaloid lycopodine (III)[6] also yields 7-methylquinoline on dehydrogenation with supported palladium[7], presumably by cleavage as indicated by the dashed lines in III. If we make the likely assumption that both lycopodine and the obscurines arise from the same biogenetic precursor, such as IV, then condensation of IV with ammonia, or its biological equivalent, at the oxygenated carbons, followed by N-methylation, leads to structure V and VI for α- and β-obscurine, respectively.

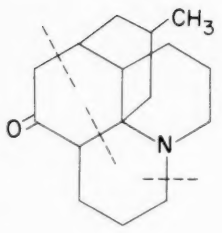
Structure V and VI explain all the known chemistry of the obscurines. Thus, partial structures I and II are incorporated and dehydrogenation with cleavage (dashed lines in V) analogous to that in lycopodine leads to 6-methyl-α-pyridone and 7-methyl-quinoline.

The NMR spectrum of β-obscurine is somewhat anomalous in that the $\geq CHCH_3$ peak (at 9.17 ppm relative to tetramethyl silane as an internal standard) is unsplit, whereas in α-obscurine the peak (at 9.14 ppm) is split.

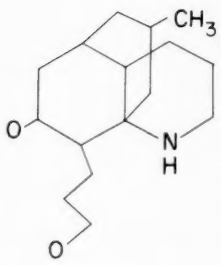
---

[6] D. B. MacLean and W. A. Harrison, in the press. We would like to thank Dr. MacLean for a copy of this paper previous to its appearance in print.

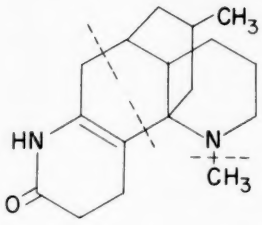
[7] L. Marion and R. H. F. Manske, Canad. J. Research, B, 20, 153 (1942).



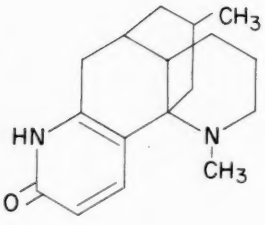
III



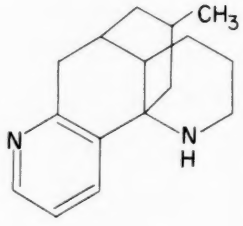
IV



V



VI



VII

The Lycopodium alkaloid lycodine[3] appears to be closely related to the obscurines. It has been shown[3] that lycodine contains a 2,3-disubstituted pyridine ring fused to a cyclohexane ring, a C-methyl group, and a secondary amino group. The analytical results quoted[3] do not exclude a molecular formula $C_{16}H_{22}N_2$ for lycodine and it is attractive to speculate that this alkaloid is formed by the same biogenetic path as the obscurines,

except that N-methylation has not occurred, and that lycodine is represented by structure VII.

Further support for the α-obscurine structure is provided by the recent elucidation[8] of the structure of selagine, a very closely related α-pyridone type of Lycopodium alkaloid.

This work was supported by a grant from the National Research Council of Canada.

---

[8] Z. Valenta, H. Yoshimura, E. R. Rogers, M. Ternbah and K. Wiesner. Tetrahedron Letters No. 10, 26 (1960), following paper.

Tetrahedron Letters No. 10, pp. 26-33, 1960. Pergamon Press Ltd. Printed in Great Britain.

THE STRUCTURE OF SELAGINE

Z. Valenta,[1] H. Yoshimura,[1,3] E. F. Rogers,[2]
M. Ternbah[1,4] and K. Wiesner[1]

[1]Organic Chemistry Laboratory
University of New Brunswick, Fredericton, Canada

[2]Merck Sharp and Dohme Research Laboratories
Division of Merck and Co. Inc., Rahway, New Jersey

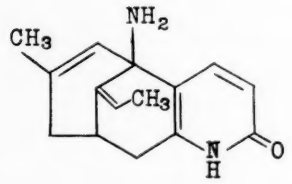
(Received 22 March 1960)

THE results of our investigation of the alkaloid selagine, isolated from Lycopodium selago, can be rationalized by the complete structure I. Selagine, m.p. 224-226°, $[\alpha]_D^{25}$ = -99° (CH_3OH) (Found: C, 73.82; H, 7.58; O, 6.73; N, 11.81; C-CH_3, 10.23. $C_{15}H_{18}ON_2$ requires C, 74.35; H, 7.46; O, 6.63; N, 11.56; 1 C-CH_3, 6.2), contains an α-pyridone grouping (λ_{max} (C_2H_5OH) 231 mμ, ε 10700; 313 mμ, ε 8500; ν max ($CHCl_3$) 1653, 1620, 1553 cm^{-1}), a basic nitrogen atom (pK_a = 7.18) and two C-methyl groups. Reduction of the alkaloid with Adams catalyst in acetic acid gave tetrahydroselagine (II), m.p. 260° (Found: C, 72.87; H, 8.80; O, 6.40; N, 11.49. $C_{15}H_{22}ON_2$ requires C, 73.14; H, 9.00;

---

[3] Holder of an N.R.C. postdoctoral fellowship on leave from Kyushu University, Japan.

[4] Holder of an N.R.C. postdoctoral fellowship on leave from the University of Zagreb, Yugoslavia.



I

O, 6.49; N, 11.37), while a similar reduction in ethanol yielded dihydroselagine (III), m.p. 260-265° (Found: C, 73.82; H, 8.35; O, 6.97; N, 11.41. $C_{15}H_{20}ON_2$ requires C, 73.74; H, 8.29; O, 6.55; N, 11.46). The fact that I, II and III have identical ultraviolet spectra shows that selagine contains two isolated double-bonds in addition to the α-pyridone grouping, and is therefore tricyclic. This conclusion is supported by NMR spectra, which also give valuable information about the substitution of the α-pyridone ring. [5] The low-field region of the spectrum of II contains only two doublets at 946 and 999 cycles/sec. corresponding to two pyridone protons (J_{H-H} = 8.5 cycles/sec.). The spectrum of selagine contains, in addition to the pyridone peaks, a multiple peak at 1039 cycles/sec.

---

[5] All NMR spectra, with the exception of pyridine (VII), were measured in $CDCl_3$ with a 56.4 Mc. Varian instrument and toluene as an external reference. The chemical shifts are recalculated to the 40 Mc. scale with the aromatic proton of toluene set arbitrarily at 1000 cycles/sec.

with an integrated surface corresponding to 2 protons and dihydroselagine shows a singlet at 1045 cycles/sec. (1 proton). Selagine therefore contains a disubstituted pyridone ring and the two remaining double-bonds are both trisubstituted. The singlet at 1045 cycles/sec. in the spectrum of dihydroselagine indicates that there is no hydrogen in the position α to the vinylic hydrogen in this compound.

The high-field portions of the NMR spectra of I, II and III revealed the relative position of the two unconjugated double-bonds and the two methyl groups in selagine. While the peak corresponding to protons with the greatest shielding is situated at 1192 cycles/sec. in selagine, dihydroselagine shows one peak with an area of 3H at 1215 cycles/sec., and tetrahydroselagine two peaks at 1216 and 1227 cycles/sec., each with an area of 3H. Both isolated double-bonds in selagine are therefore directly joined to a methyl group. Additional information about the environment of the double bonds was obtained by the oxidation of I, II and III under Kuhn-Roth conditions followed by steam distillation and chromatography of the volatile acids on silicic acid according to Marvel and Rands. [6] Selagine

[6] C. S. Marvel and R. D. Rands, Jr., J. Amer. Chem. Soc. 72, 2642 (1950).

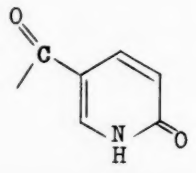
1960

gave only acetic acid, while dihydro- and tetrahydroselagine yielded propionic acid and acetic acid under the same conditions. Compounds II and III therefore contain an ethyl group, while selagine itself must contain an ethylidene grouping and an endocyclic double-bond substituted in the way indicated in structure I.

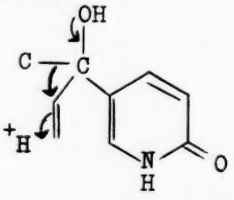
Treatment of selagine with nitrous acid gave selaginol (IV), m.p. 265-267°, $[\alpha]_D^{25} = -103°$ (CH_3OH) (Found: C, 73.40; H, 7.19; O, 13.63; N, 5.78. $C_{15}H_{17}O_2N$ requires C, 74.04; H, 7.04; O, 13.15; N, 5.76). The similarity of rotation and ultraviolet, infrared and NMR spectra of IV and I indicated that no rearrangement had occurred during the diazonium ion decomposition. Catalytic reduction of selaginol gave tetrahydroselaginol (V), m.p. 236-238° (Found: C, 72.86; H, 8.57; O, 12.99; N, 5.64. $C_{15}H_{21}O_2N$ requires C, 72.88; H, 8.50; O, 12.96; N, 5.67), which on treatment with phenylphosphonic dichloride yielded an oily dichlorocompound (VI) (ν max ($CHCl_3$) 1577, 1563 cm^{-1}; no OH or α-pyridone peaks in the IR spectrum). Catalytic reduction of VI removed both chlorine atoms and gave the oily pyridine (VII) which was purified through a crystalline picrate, m.p. 154-158°, and by distillation (Found: C, 83.61; H, 9.99; N, 6.64. $C_{15}H_{21}N$ requires C, 83.67; H, 9.83; N, 6.50). The NMR spectrum of compound VII (a

quartet at -144 cycles/sec. for α-hydrogen; an unsymmetrical doublet at -108 and -103 cycles/sec. for γ-hydrogen; an unsymmetrical quartet at -95 to -87 cycles/sec. for β-hydrogen; Jα-β = 4.5 cycles/sec.; Jα-γ = 1.5 cycles/sec.; Jβ-γ = 8 cycles/sec.) clearly showed the presence of a 2,3-disubstituted pyridine ring. [7] Selagine must therefore contain a 5,6-disubstituted α-pyridone ring.

While selagine was completely inert to 6N hydrochloric acid, treatment of selaginol with concentrated hydrochloric acid yielded the ketone (VIII), m.p. 268-270° (Found: C, 73.69; H, 7.04; O, 13.94; N, 5.77. $C_{15}H_{17}O_2N$ requires C, 74.04; H, 7.04; O, 13.15; N, 5.76). The ultraviolet spectrum of VIII (λ_{max} (C_2H_5OH) 284 mμ, ε 19300) indicated the presence of the chromophore (VIIIa).



VIIIa



VIIIb

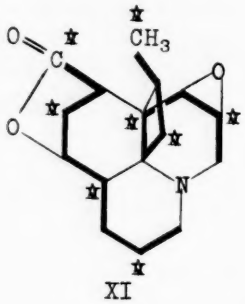
[7] The spectrum was taken with a 40 Mc. Varian instrument in $CDCl_3$. The chemical shifts are calculated (at 40 Mc./sec. frequency) relative to water. For comparison, see e.g., F.A.L. Anet and C.R. Eves, Canad. J. Chem. 36, 902 (1958).

1960

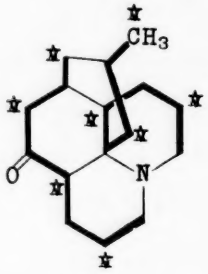
Catalytic reduction of VIII followed by a reduction with sodium borohydride yielded the alcohol (IX), m.p. 203-205° (ultraviolet spectrum identical with V) (Found: C, 71.91; H, 8.31; O, 13.65; N, 5.60. $C_{15}H_{21}O_2N$ requires C, 72.88; H, 8.50; O, 12.96; N, 5.67), which was not identical with tetrahydroselaginol (V). The possibility that the formation of the ketone (VIII) involved a skeletal rearrangement was supported by the finding that the hydroxyl group in tetrahydroselaginol (V) could not be oxidized with chromium trioxide in acetic acid or acetylated in boiling acetic anhydride/sodium acetate. The primary amino group of selagine is therefore attached to a tertiary carbon atom. The formation of the ketone (VIII) can be formulated as indicated in the structure VIIIb and it establishes the relative position of the primary amino group, the α-pyridone ring, and one of the two double-bonds in selagine.

Dehydrogenation of selagine with palladium on charcoal at 300° yielded 6-methyl-2-pyridone; dehydrogenation with selenium at 320° yielded an oily base (X) characterized as a crystalline picrate, m.p. 195-198° (Found: C, 58.29; H, 4.00. $C_{21}H_{16}O_7N_4$ requires C, 57.79; H, 3.69). Base (X) is an azaanthracene (ultraviolet spectrum) and on the basis of its analysis and the proposed structure I for selagine can be formulated as 5,7-dimethyl-1-azaanthracene.

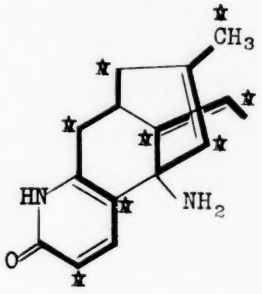
A close inspection of structure I and the structure of annotinine (XI) [8] and lycopodine (XII) [9] reveals an interesting biogenetic relationship. The biogenesis of annotinine (XI) is best visualized as the condensation of



XI



XII



XIII ≡ I

two eight-carbon chains (each formed from 4 acetate units). [10,11] Lycopodine is then built up on the same

---

[8] K. Wiesner, Z. Valenta, W.A. Ayer and C. Bankiewicz, Chem. and Ind. 1019 (1956); K. Wiesner, W.A. Ayer, L.R. Fowler and Z. Valenta, Chem. and Ind. 564 (1957); K. Wiesner, Z. Valenta, W.A. Ayer, L.R. Fowler and J.E. Francis, Tetrahedron 4, 87 (1958); M. Przybylska and F.R. Ahmed, Acta Cryst. 11, 718 (1958).

[9] Formula (XII) was proposed for lycopodine by Dr. D.B. McLean, McMaster University, Canada. (Private communication)

[10] When structure XI was first proposed for annotinine at the U.N.B. summer seminar (Grand Manan, 1956), Professor H. Conroy proposed this ingenious biogenetic possibility. (H. Conroy, forthcoming communication)

[11] ''Methyl'' carbons are marked with an asterisk.

1960

principle and differs from annotinine only by a different condensation of the two chains. Selagine (XIII ≡ I) differs from lycopodine only by the attachment of one of the chains to another nitrogen atom and by the absence of a terminal carboxyl group in the other chain. The clarification of the structure of α- and β-obscurine by W. A. Ayer et al. [12] establishes these two alkaloids as biogenetic links between lycopodine and selagine.

---

[12] W. A. Ayer and G. G. Iverbach, Tetrahedron Letters No. 10, 19 (1960), preceding paper.

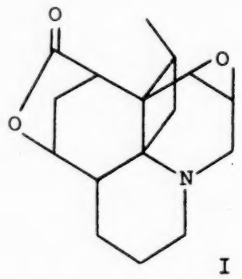
Tetrahedron Letters No. 10, pp. 34-37, 1960. Pergamon Press Ltd. Printed in Great Britain.

BIOGENESIS OF *LYCOPODIUM* ALKALOIDS[1]

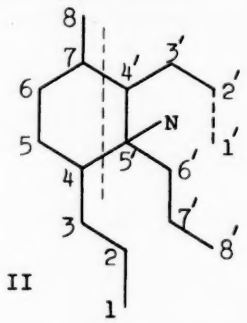
Harold Conroy
Department of Chemistry, Yale University, New Haven, Conn.

(Received 4 April 1960)

IN 1956, shortly after the brilliant elucidation of structure of the *Lycopodium* alkaloid annotinine (I) by Wiesner, Valenta and their coworkers[2], we considered that



I



II

the skeleton inherent in I might owe its biogenetic derivation to the condensation of two eight-carbon

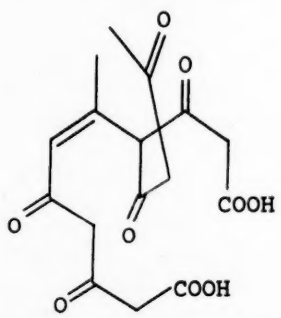
---

[1] Contribution number 1612 from the Sterling Chemistry Laboratory at Yale University.

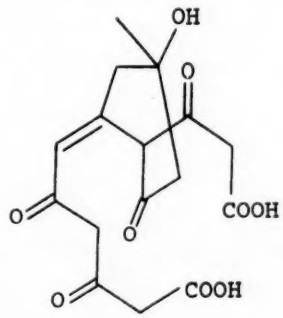
[2] K. Wiesner, Z. Valenta, W. A. Ayer and C. Bankiewicz, *Chem. and Ind.* 1019 (1956); K. Wiesner, W. A. Ayer, L. R. Fowler and Z. Valenta, *Chem. and Ind.* 564 (1957); K. Wiesner, Z. Valenta, W. A. Ayer, L. R. Fowler and J. E. Francis, *Tetrahedron* 4, 87 (1958); *Cf.* M. Przybylska and F. R. Ahmed, *Acta Cryst.* 11, 718 (1958).

polyacetate straight chains of the type believed to play a part, for example, in fatty acid biosynthesis, or in the formation of macrolide antibiotics[3]. With the recent elaboration of structures of further alkaloids of this class, notably selagine[4], lycopodine[5], lycodine[6] and the obscurines[6], whose formulae are all based upon the framework (II), this hypothesis is seen to gain support. A speculative biosynthesis beginning with two molecules of a 3,5,7-triketo-octanoic acid equivalent accounts not only for the grosser aspects (II) but for many structural details as well. Of course, while the scheme is plausible enough, it will nontheless require experimental scrutiny.

The order of steps is somewhat uncertain; however the sequences shown will serve for illustration. The common i ermediate (III) results from aldol condensation between the C-7 carbonyl and the C-4′ methylene, followed by dehydration. A second aldol condensation links C-8 and C-7′,



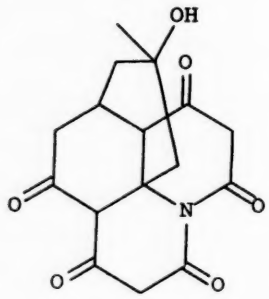
III



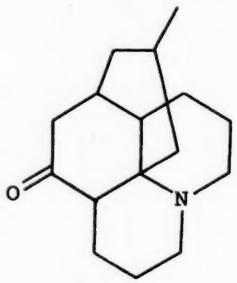
IV

[3] R.B. Woodward, Angew. Chem. 69, 50 (1957).
[4] Z. Valenta, H. Yoshimura, E.F. Rogers, M. Ternbah and K. Wiesner, Tetrahedron Letters No. 10, 26 (1960).
[5] D.B. MacLean and J.A. Harrison, In press. Cf. ref. 4.
[6] W.A. Ayer and G.G. Iverach, Tetrahedron Letters No. 10, 19 (1960).

as in (IV), and after reduction of the double bond, Mannich condensation with an ammonia molecule joins C-4 and C-5'. Completion of both δ-lactam rings gives (V), and further reduction at carbons 1, 1', 3, 3', and 7' results in lycopodine (VI)[5].

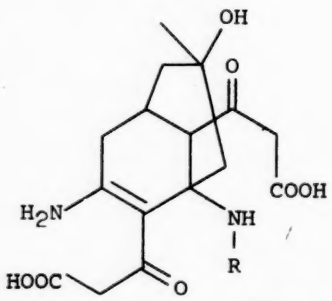


V

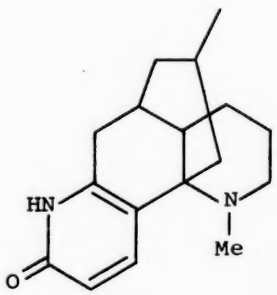


VI

Similarly, formation of the obscurines requires the intermediate (VII), where the first nitrogen has been methylated and the second nitrogen has been introduced at the site of the C-5 carbonyl. After lactam closure and removal of oxygen we have the pyridone (VIII) (β-obscurine)[6],



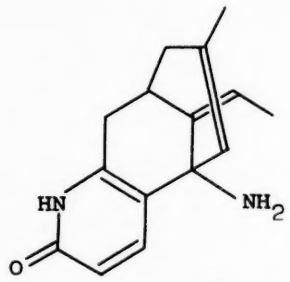
VII, R = Me
X, R = H



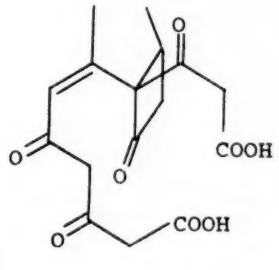
VIII

the corresponding dihydropyridone (α-obscurine), or the pyridine (lycodine)[6].

In the case of selagine (IX)[4], we proceed from X, but the carboxyl carbon (C-1′) is lost (decarboxylation of a β-ketoacid) signs of unsaturation at C-3′ and C-7′ are still present in the final alkaloid.



IX



XI

The scheme for annotinine (I) represents only a minor deviation from these pathways. We suggest that, in III or at least prior to the formation of IV, the methyl carbon C-8 becomes oxidized to the level of carboxyl. With aldolization at C-8 prohibited, an alternative involves closure at C-4′, with formation of the cyclobutane ring of XI. Again, Mannich condensation and lactamization (as in IV ⟶ V), adjustment of oxidation state and, in this case, lactonization, results in the naturally occurring alkaloid (I).

It is a fact that each and every oxygenated position of the postulated two 3,5,7-triketooctanoic acid precursor molecules either i) takes a direct part in the formation of the final skeleton or ii) can otherwise be accounted for as an oxygenated or unsaturated center in one or the other of the final alkaloids.

We wish to thank Professor Wiesner for many stimulating discussions and for the opportunity to read his manuscript in advance of publication.

Tetrahedron Letters No. 10, pp. 38-40, 1960. Pergamon Press Ltd. Printed in Great Britain.

ADDITION OF CHLOROCARBENE TO BENZENE

Gerhard L. Closs and Liselotte E. Closs

Department of Chemistry, The University of Chicago

Chicago 37, Ill.

(Received 31 March 1960)

Recently, we reported the formation of chlorocarbene from methylene chloride and alkyllithium compounds and its addition to olefins to yield chlorocyclopropanes.[1] The reactivity of the carbene was established, as expected, to be intermediate between methylene and dichlorocarbene through competitive experiments involving olefins.[2] In this connection it was of interest to examine the addition of chlorocarbene to benzene, a reaction which dichlorocarbene fails to undergo.[3]

When methyllithium was slowly added to a refluxing solution of benzene in methylene chloride, 7-methylcyclohepta-1,3,5-triene (III) (b.p. 132.5; n_D^{20} 1.5030; UV_{EtOH} λ_{max} 257 mμ, ϵ 3600; anal. calc. C_8H_{10} C 90.50, H 9.50, found C 90.27, H 9.81) was isolated in 20% yield.[4] Assignment of structure III to

---

(1) G.L. Closs and L.E. Closs, J. Am. Chem. Soc. 81, 4996 (1959).

(2) G.L. Closs and G.M. Schwartz, ibid., in press.

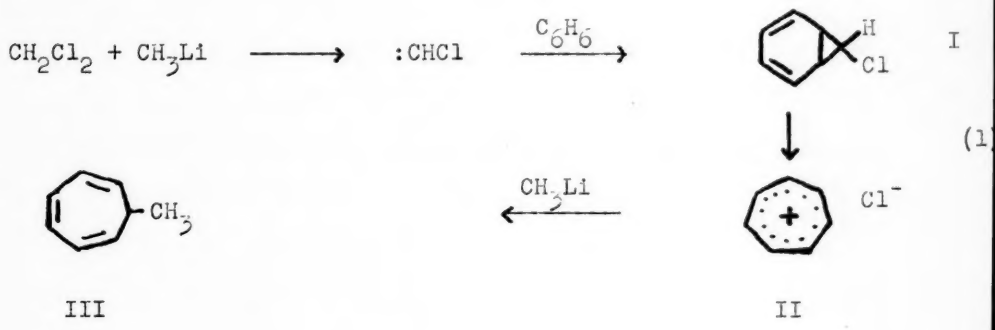
(3) W.v.E. Doering and Wm. A. Henderson, ibid. 80, 5274 (1958).

(4) The three other isomers of methylcycloheptatriene have been reported recently by N.A. Nelson, J.H. Fassnacht and J.U. Piper, ibid. 81, 5009 (1959).

1960

the reaction product is based on catalytic hydrogenation to methylcycloheptane and the nuclear magnetic resonance spectrum which shows a doublet at 210 and 216 c.p.s. (relative to external benzene at 40 mc) indicating the attachment of the methyl group at a saturated carbon atom.

The mechanism for the formation of III is formulated in reaction sequence 1: Chlorocarbene, generated from methylene chloride and methyllithium, adds to benzene to form the hypothetical intermediate I. This adduct undergoes a valence tautomerization to tropylium chloride (II) which adds methyllithium to give 7-methylcyclohepta-1,3,5-triene (III).[5]



Tropylium chloride (<1%), identified by its characteristic ultraviolet spectrum was detected in the acidified, aqueous washings

(5) The addition of phenyllithium to tropylium bromide proceeds smoothly to yield 7-phenylcyclohepta-1,3,5-triene, W.v. Doering and L.H. Knox, J. Am. Chem. Soc. 75, 297 (1953).

of the reaction mixture. Apparently, only a small quantity of the chloride escapes further reaction with methyllithium. In contrast to the reaction of methylene with benzene[6] no products resulting from insertion of the carbene into carbon-hydrogen bonds are observed and the product is obtained free of isomers.

The main fraction of the generated chlorocarbene is lost in the competing reaction with methyllithium leading to the formation of ethylene, summarized in sequence 2.[7]

$$CH_3Li + :CHCl \longrightarrow \underset{IV}{CH_3CHClLi} \longrightarrow \underset{V}{CH_3\text{-}\ddot{C}H} \longrightarrow CH_2{=}CH_2 \qquad (2$$

It can be argued that III is formed by the addition of methylcarbene (V) to benzene. However, this possibility is rendered unlikely in view of the observation that adducts of methylcarbene are not formed when olefins are employed as the substrate. Presumably the intramolecular hydride shift in methylcarbene is too fast to allow an intermolecular process to compete successfully.

---

(6) W.v.E. Doering and L.H. Knox, J. Am. Chem. Soc. 75 (1953).

(7) For the equivalent reaction of chlorocarbene with n-butyllithium, see ref. 1.

1960

Tetrahedron Letters No. 11, pp. 1-4, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

ACETESSIGSÄURE-DITHIOKETALE

Heinrich Hauptmann und Aurora Catharina Giora[1]

Departamento de Química, Faculdade de Filosofia, Ciências e Letras da Universidade de São Paulo, Brasil

(Received 7 April 1960)

ACETESSIGSÄURE-DITHIOKETALE sind, abgesehen der β,β-Bis-[carboxy-methylthio]-buttersäure die durch vorsichtige Verseifung ihres Äthylesters dargestellt worden ist,[2] in reiner Form nicht bekannt.[3] An ihrer Stelle wurden stets die zuerst von Baumann[4] beschriebenen, am Schwefel substituierten β-Mercaptocrotonsäuren erhalten. Es gelingt jedoch leicht, diese Verbindungen durch Anlagerung von Mercaptanen in Gegenwart von Piperidin und Pyridin[5] in Acetessigsäure-dithioketale überzuführen.

Auch die Verseifung der Acetessigester-dithioketale mit maximal 1,2 Äquivalenten Alkali führt ohne Mercaptanabspaltung zu den Dithioketalen der freien Säure. Die Verseifung der Carbäthoxygruppe läuft also unter diesen Bedingungen mit weit grösserer Geschwindigkeit ab als die Eliminierungreaktion, sodass sie beendet ist, ehe letztere merkbar wird.

---

[1] Aus der "Tese de doutoramento" von A.C. Giora, São Paulo (1960).

[2] B. Holmberg, J. Prakt. Chem. (2) 135, 57 (1932).

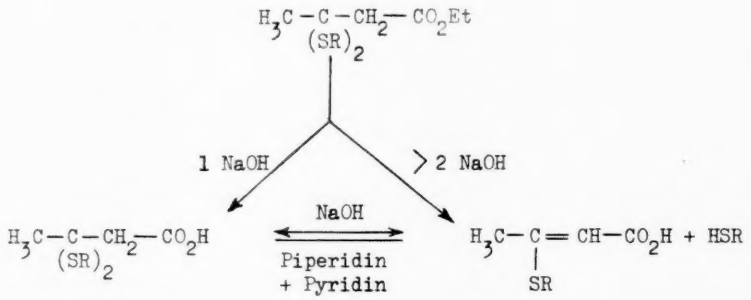
[3] Th. Posner, Ber. 32, 2801 (1899); 34, 2643 (1901).

[4] R. Escales und E. Baumann, Ber. 19, 1787 (1886).

[5] S. Ruhemann, J. Chem. Soc. 77, 1120 (1900); H. Fiesselmann, Ber. 87, 835, 841 (1954); B. Wladislaw, Chem. & Ind. 263 (1957).

TET.11/A

Die Acetessigsäure-dithioketale, von denen einige in der Tabelle aufgeführt sind, sind kristallisierte, in reinem Zustand beständige Verbindungen; die von Säuren bereits bei Zimmertemperatur langsam zersetzt werden.



Erhitzt man sie in alkalischer Lösung, so wird ein Mol Mercaptan abgespalten, und es entstehen β-Alkylthio- bzw. β-Arylthio-crotonsäuren. Aus gemischten Dithioketalen, z.B. aus der β-Äthylthio-β-phenylthio-buttersäure, wird in der Regel ein Merkaptan bevorzugt abgespalten, wobei die in der Tabelle aufgeführten Ergebnisse folgende Sequenz hinsichtlich der Geschwindigkeit der Abspaltung erkennen lassen:

$$H_5C_6\text{-S-} > H_5C_2\text{-S-} \cong H_5C_6\text{-}CH_2\text{-S-} > HO_2C\text{-}CH_2\text{-S-}$$

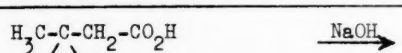
Wenn man von Thioglykolsäure enthaltenden Dithioketalen ausgeht, so erhält man die β-Carboxymethylthio-crotonsäure allerdings nur in verhältnismässig geringer Ausbeute, da im Einklang mit Fiesselmanns Beobachtungen[6] hauptsächlich Ringschluss zur 3-Hydroxy-5-methyl-thiophen-2-carbonsäure vom Schm. 122° eintritt, die zur Identifizierung in ihren bekannten Methylester[7]

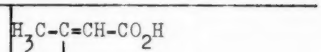
---

[6] H. Fiesselmann und G. Pfeiffer, Ber. 87, 848 (1954).

[7] H. Fiesselmann und F. Thoma, Ber. 89, 1907 (1956), s.a.D.B.P. 1.020.641; Chem. Abstr. 54, 2357b (1960).

vom Schm. 51° übergeführt wurde.





R	R'	Schmp	Ausb %	% S ber	% S gef	Aqu. ber	Aqu. gef	R	Schmp	Ausb %
Ät	Ät	68°	70	30,76	30,52	208	208	Ät[8]	91°	92
Ph	Ph	76°	30	21,05	21,22	304	304	Ph[4]	142°	75
Bz	Bz	82°	50	19,27	18,87	332	332	Bz[9]	130°	88
Ät	Ph	65°	60	25,00	25,27	256	250	Ät	91°	80
Ät	Bz	84°	65	23,70	23,40	270	270	Ät + Bz	91° 130°	30 45
Ät	Cbmet	95°	60	26,88	26,74	119	118	Cbmet	157-158°	15 *

Ät = Äthyl, Ph = Phenyl, Bz = Benzyl, Cbmet = Carboxymethyl

* Nebon 53% 3-Hydroxy-5-methyl-2-thiophencarbonsäure.

Dithioketale des Acetessigesters zeigen, wenn sie mit einem grösseren Überschuss an Alkali verseift werden, ein völlig analoges Verhalten.

Einige kürzlich erschienene Veröffentlichungen haben sich mit der "Festigkeit" der Kohlenstoff-Schwefel Bindung in Thioäthern und verwandten Verbindungen befasst,[10] wobei Knunyants auch Dithioketale des Acetessigsäureamids in den Bereich seiner Untersuchungen einbezogen hat.

Die gemischten Thioketale der Acetessigsäure bzw. ihres Esters erlauben

---

[8] W. Autenrieth, Liebigs Ann. 254, 234 (1889).

[9] W. Autenrieth, Ber. 29, 1639 (1896).

[10] I.L. Knunyants und N.P. Gambaryan, Izv. Akad. Nauk SSSR, Otdel Khim. Nauk 1219 (1958); Chem. Abstr. 53, 4193d (1959). M. Kulka, Canad. J. Chem. 37, 325 (1959); Chem. Abstr. 53, 21765d (1959). K.J. Morgan, J. Chem. Soc. 3502 (1959).

also den direkten Vergleich verschiedener Alkyl- oder Arylmercaptogruppen, hinsichlich der Geschwindigkeit, mit der sie von demselben Kohlenstoff abgespalten werden und zeigen somit den Einfluss der am Schwefel haftenden Substituenten auf die "Festigkeit" der Kohlenstoff-Schwefel Bindung. Da diese wahrscheinlich von den Reaktionsbedingungen abhängt ist beabsichtigt, das Verhalten einer Reihe von geeigneten Verbindungen dieses Typs bei Eliminierungsreaktion unter verschiedenen Bedingungen zu untersuchen.

Wir danken der Rockefeller Foundation, New York, und dem Conselho Nacional de Pesquisas, Rio de Janeiro, für die materielle Unterstützung dieser Arbeit, letzterem ausserdem für ein Stipendium für A.C.G.

Tetrahedron Letters No. 11, pp. 5-9, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

ISOMERIZATIONS IN THE DICYCLOPENTADIENE SERIES

P. Yates and P. Eaton

Department of Chemistry, Harvard University, Cambridge, Mass.

(Received 7 April 1960)

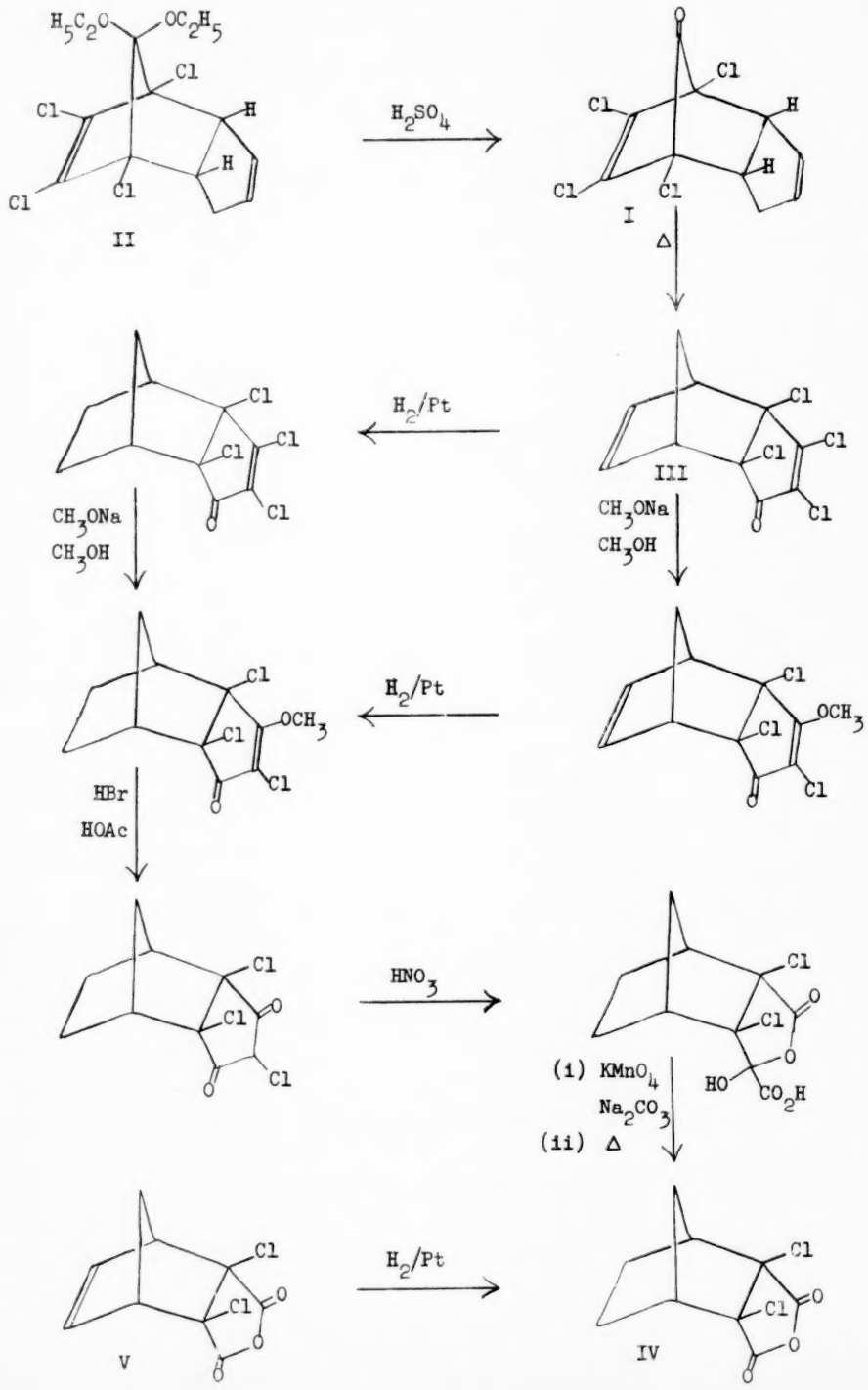
RECENT interest in the thermal rearrangement of dicyclopentadiene alcohols[1] and in the chemistry of related polychloroketones[2] leads us to give a preliminary report on experiments concerned with the isomerization of 4,5,6,7-tetrachloro-3a,4,7,7a-tetrahydro-4,7-methanoinden-8-one (I), m.p. 123-123.5°, $\lambda_{max}^{CCl_4}$ 3.34, 5.48, 6.33 μ (Found: C, 42.32; H, 2.05; Cl, 49.86. $C_{10}H_6Cl_4O$ requires: C, 42.29; H, 2.13; Cl, 49.94), prepared by hydrolysis of the adduct (II)[3] from cyclopentadiene and 1,2,3,4-tetrachloro-5,5-diethoxycyclopentadiene. When I was heated at 135° for 1 hr it was converted in quantitative yield to an isomer, m.p. 82-83°, $\lambda_{max}^{CCl_4}$ 3,23, 3.31, 5.73, 6.30 μ, λ_{max}^{EtOH} 255 mμ (ε 9100) (Found: C, 42.53; H, 2.14, Cl, 49.86). This is formulated as III on the basis of the spectral data and its conversion to IV, m.p. 202-203° (sealed cap.), $\lambda_{max}^{CCl_4}$ 5.28, 5.36, 5.53 μ (Found: C, 46.04; H, 3.67; Cl, 29.89. $C_9H_8Cl_2O_3$ requires C, 45.98; H, 3.43; Cl, 30.17), which was shown to be identical with the product obtained by hydrogenation of the

---

[1] R.B. Woodward and T.J. Katz, Tetrahedron 5, 70 (1959).

[2] K. MacKenzie, J. Chem. Soc. 473 (1960).

[3] C.A. Peri, Gazz. Chim. Ital. 85, 1118 (1955).


H5C2O
OC2H5
Cl
H
II
H2SO4
I
Δ
H2/Pt
III
CH3ONa
CH3OH
OCH3
HBr
HOAc
HNO3
(i) KMnO4
Na2CO3
(ii) Δ
HO
CO2H
V
IV

1960

adduct (V) of dichloromaleic anhydride and cyclopentadiene.[4] The route used for the conversion of III to IV is shown in the annexed scheme (all intermediate compounds have been characterized by satisfactory elementary analyses and all show spectra in accord with the structures assigned). The endo configuration is assigned to II and V on the basis of analogy;[5] the endo configurations of their congeners then follow. This configuration for III is corroborated by the observation that on ultraviolet irradiation it gives a new isomer, m.p. 113.5-114.5°, $\lambda_{max}^{CCl_4}$ 5.52 μ, $\lambda_{max}^{Et_2O}$ 295 mμ (ε 30) (Found: C, 42.09; H, 1.82; Cl, 49.76) which is assigned the cage structure VI.[6]

The rearrangement of I to III is reminiscent of the thermal rearrangement of hydroxydicyclopentadienes recently investigated by Woodward and Katz.[1,7] Although we lack the elegant stereochemical arguments developed by these investigators, we consider that the facility of the reaction and the absence of other products make it very likely that the reaction proceeds by a route analogous to that proposed by them for the hydroxydicyclopentadienes, i.e. via VII. The complete conversion of I to III and our failure to observe the reverse reaction must reflect the fact that III is strongly favored in the equilibrium I $\rightleftharpoons$ III. This is consonant with the expected greater

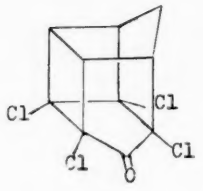
---

4 A.M. Clifford and C.E. Gleim, U.S. Pat. 2,391,226 (1945); cf. Chem. Abstr. 40, 3136 (1946).

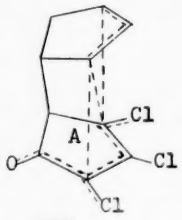
5 M.C. Kloetzel, Organic Reactions Vol. IV, p. 11. John Wiley, New York (1948); K. Alder and M. Schumacher, Fortschr. Chem. Naturstoffe 10, 17 (1953).

6 Cf. R.C. Cookson, E. Crundwell and J. Hudec, Chem. & Ind. 1003 (1958); R.C. Cookson and E. Crundwell, Ibid. 1004 (1958).

7 As pointed out by these authors, these reactions are special cases of the Cope rearrangement; cf. E.G. Foster, A.C. Cope and F. Daniels, J. Amer.Chem.Soc. 69, 1893 (1947); and earlier papers.



VI



VII

stability of III, in which the carbonyl group is conjugated and also is relieved in part of the considerable angle strain attendant upon its placement at the single carbon bridge in I.

In the present case, the carbonyl group and chlorine atoms would be expected to lead to an unusually high polarization of the electronic displacements in VII, resulting in a considerable net negative charge on ring A. It was therefore of considerable interest to find that the isomerization of I to III was accelerated by sulfuric acid and by Lewis acids. Indeed, in the presence of a large excess of aluminum chloride at room temperature, I in solution in carbon tetrachloride was converted completely to III within three minutes. The spectacular acceleration of this conversion can be rationalized in terms of the formation of a complex between the aluminum chloride and the carbonyl oxygen atom; this should greatly facilitate the bond-breaking process symbolized in VII. We plan to investigate further the effect of Lewis acids on this and related reactions in the hope of obtaining results of both mechanistic and synthetical import.[8]

---

[8] In this connection, it is of interest that several examples of catalysis of the Diels - Alder reaction by acids have been reported.[9]

[9] A. Rodgman and G.F. Wright, J. Org. Chem. 18, 465 (1953); W. Rubin, H. Steiner and A. Wasserman, J. Chem. Soc. 3046 (1949), and earlier papers; L.E. Gast, E.W. Bell and H.M. Teeter, J.Amer.Oil Chem.Soc. 33, 278 (1956).

Acknowledgements - Part of this work was carried out during the tenure of a National Science Foundation Cooperative Fellowship by P.E. We are greatly indebted to the General Chemical Division, Allied Chemical Corporation, for a grant which defrayed the cost of this investigation.

1960

Tetrahedron Letters No. 11, pp. 10-14, 1960. Pergamon Press Ltd. Printed in Great Britain.

ZUR THERMISCHEN ISOMERISATION VON CITRAL

G. Ohloff

Max-Planck-Institut für Kohlenforschung,
Abtlg. Strahlenchemie, Mülheim/Ruhr

(Received 12 April 1960)

Natives und synthetisch gewonnenes Citral stellen stets eine Mischung von 2 Stereoisomeren des 2,6-Dimethyl-octadien-2,6-als-(8)[1] dar. In diesen Gemischen ist das mit dem Trivialnamen Geranial (I) belegte trans-Isomere gegenüber der cis-Form Neral (II) stets in überwiegender Menge vorhanden[2]. Obwohl Citral eine sehr oft untersuchte Verbindung ist, blieb seine thermische Isomerisierung bisher unbekannt.

Wir fanden, daß ein Geranial(I)-Neral(II)-Gemisch (2:1) bereits beim Erhitzen auf 130° unter Sauerstoffausschluß

---

[1] E. Gildemeister, Die Ätherischen Öle, Verlag der Schimmel u. Co. A.G., Miltitz bei Leipzig, Bd.I. S.509 (1928). J.L. Simonsen u. L.N. Owen, The Terpenes. At the University Press, Cambridge, Vol.I, p.83 (1947).

[2] F. Tiemann, Ber.dtsch.Chem.Ges. 33, 883 (1900); Y.R. Naves u. A. Ödermatt, Bull.Soc.Chim.France 1958, 377; Compt.rend. 247, 687(1958); Y.R.Naves u. A.V. Grampoloff, Compt.rend 248, 2029(1959). F. Porsch u. H. Farnow, Dragoco Ber. 1959, 248 s. dort weitere Literatur. Vgl. auch Fußnote 1.

1960

langsam in Isocitral (VIII u. IX) übergeht. Diese Umlagerung kann praktisch quantitativ durchgeführt werden, wenn man Citral an einer Glockenboden-Kolonne bei 15 Torr (Bodentemp. 130°) unter Argonschutz mehrfach destilliert (Rücklaufverhältnis 1:10). Im Destillat werden VIII u. IX jedesmal in 25-proz. Ausbeute angereichert. Analytisch kann das Fortschreiten der Isomerisation mit Hilfe der IR-Spektren verfolgt werden, wozu sich besonders die Auswertung der bei 1724 cm^{-1} auftretenden st C=O-Schwingung einer isolierten Carbonylgruppe eignet.

Bei Steigerung der Bodentemp. auf 160° durch Verringerung des Vakuums auf 70 Torr werden die Isocitrale (VIII u. IX) nach einmaliger Isomerisation bereits in 70-proz. Ausbeute angereichert, während bei 175° Bodentemp. (130 Torr) die Umwandlung praktisch vollständig ist. Mit der Erhöhung der Isomerisationstemp. kann man das Auftreten einer terminalen Doppelbindung (w CH_2-Schwingung bei 890 cm^{-1}) beobachten, was der Bildung von VII entspricht. So setzt sich das bei 175° gewonnene Isomerisat aus 3o% VII und 7o% eines Gemisches der Stereoisomeren VIII und IX zusammen, von denen das cis-Isomere IX lt. Gaschromatogramm die Hauptmenge ausmacht. Die Isomeren VII bis IX lassen sich destillativ anreichern. Einen Hinweis auf die Struktur von VII erhalten wir aus seiner basenkatalysierten Isomerisation zum Citral (I u. II). Damit scheidet auch eine diskutierbare thermische Isomerisation der Doppelbindung von C_2 nach C_1 aus.

4-stdg. Erhitzen von Citral auf 205° im Bombenrohr unter

TET 11/64

reinem Argon führt überraschenderweise zu einem 70-proz. Umsatz der Carbonylgruppe. Aus dem Reaktionsgemisch wurden mit Hilfe der o-Borsäureester-Methode p-Menthadienole isoliert, die wahrscheinlich aus einem Gemisch der 3 Verbindungen XI-XIII bestehen und deren Trennung wir z.Zt. betreiben. Das Alkoholgemisch tritt bereits bei der einfachen Isomerisation des Citrals auf. So bilden sich bei 130° 4%, bei 160° 8% und bei 175° 20% Alkohole $C_{10}H_{16}O$.

Bei 450° wird Isopiperitenol (XI)[3] zum Neral (II) pyrolysiert, wobei Isocitral als Isomerisationsprodukt auftritt. Analog dazu wird Isopulegol in Citronellal überführt[4].

Zum Reaktionsmechanismus.

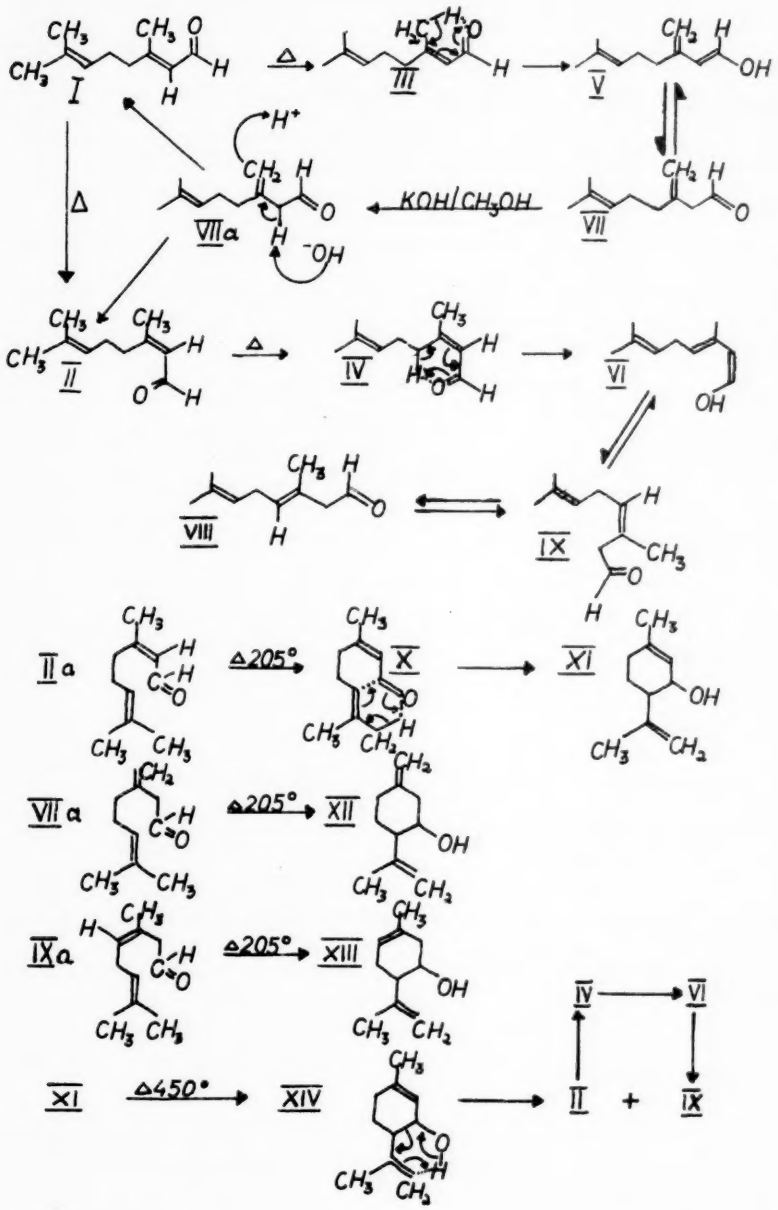
Die Verschiebung der Doppelbindung aus der Konjugation in ß,γ-Stellung vollzieht sich intramolekular unter cyclischem Elektronentransfer, gemäss Übergangszuständen III u. IV. Die Richtung der Pfeile symbolisiert hier den Übergang eines Protons vom ß-C-Atom des Aldehyds an das Carbonyl und die zwischenzeitliche Ausbildung der Enole V u. VI, die dann sofort in ihre Tautomeren VII-IX übergehen. Eine Bildung von VIII u. IX ist lediglich aus Neral (II) denkbar. Demnach muß eine thermische Isomerisation der trans-(I) in die cis-Form (II) vorausgegangen sein, die mit höherer Geschwindigkeit abläuft als die Ausbildung

---

[3] A.B.Booth u. A.E.Klein, US Patent 2 815 383 (1957).

[4] V.Grignard u. J. Doeuvre, Compt.rend. 190, 1164 (1930).

1960


I
III
V
VII
VIIa
II
IV
VI
VIII
IX
IIa
X
XI
VIIIa
XII
IXa
XIII
XI
XIV
Δ
Δ205°
Δ450°
KOH/CH3OH
H+
-OH

des cyclischen Zwischenzustandes III.

Die entdeckte thermische Cyclisierung kann ebenfalls durch einen Elektronentransfer erklärt werden, der über ein bicyclisches System der präformierten cis-Verbindungen IIa u. IXa erfolgen kann. VIIa geht nach dem gleichen Prinzip in das Menthadienol XII über. Analog dazu konnte u.a. auch der in ß,γ-Stellung partiell gesättigte Aldehyd, das (+)-Citronellal, in hohen Ausbeuten in das (-)-Isopulegol überführt werden. Die thermische Cyclisation stellt einen neuen Typ indirekt substituierender Additionsreaktionen[5] und zwar von intramolekularer Art dar.

Die Pyrolyse von ß,γ-ungesättigten Alkoholen, die als thermische Rückreaktion der Cyclisierung erkannt wurde, muß ebenfalls über einen cyclischen Mechanismus erfolgen. Als Zwischenstufe der Bildung von II aus XI ist XIV anzusehen. Im gleichen Sinne kann die Überführung des Isopulegols in Citronellal formuliert werden.

Die 3 hier untersuchten thermischen Reaktionen finden nach unseren bisherigen Kenntnissen um so schneller und eindeutiger statt, je leichter ein planarer Übergangszustand ausgebildet werden kann, was an einer Anzahl von Verbindungen gefunden wurde und worüber wir an anderer Stelle noch ausführlich berichten werden.

---

[5] K.Alder u. M.Schumacher in L.Zechmeister, Fortschritte der Chemie organischer Naturstoffe X, 11,97. Springer-Verlag Wien 1953.

Tetrahedron Letters No.11, pp. 15-17, 1960. Pergamon Press Ltd. Printed in Great Britain.

INDOLOPYRONE UND PYRIDONE

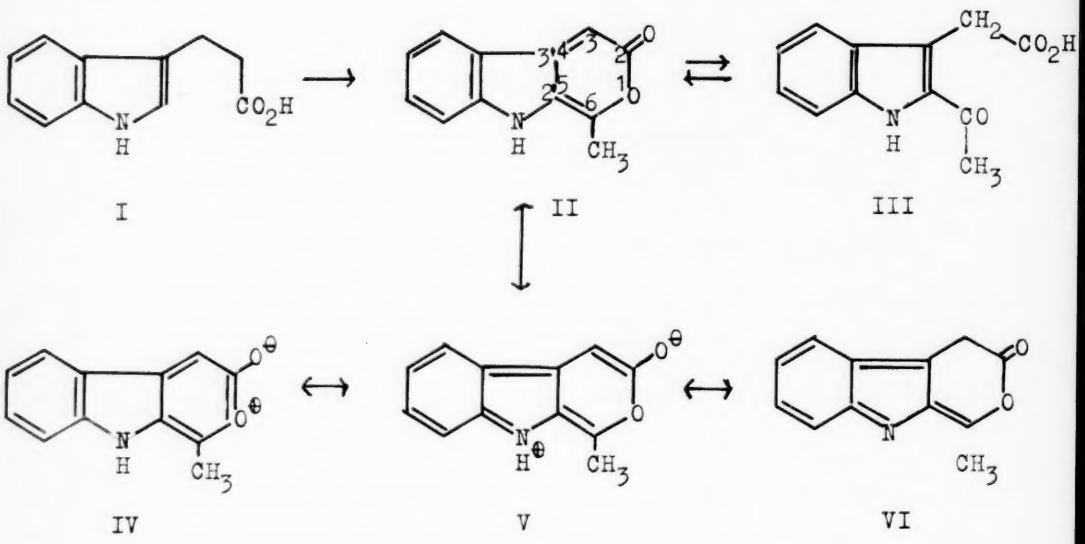
Hans Plieninger und Wolfgang Müller

Chemisches Institut der Universität Heidelberg

(Received 13 April 1960)

Setzt man Indolyl-3-essigsäure in einem Acetanhydrid-Äther-Gemisch mit Bortrifluorid-Ätherat bei 20° um, so erhält man eine gelbe Verbindung vom Schmp. 252° (aus Aceton). Die Analyse spricht für $C_{12}H_9O_2N$ (Ber. C 72.35, H 4.56, N 7.03; Gef. C 71.99, H 4.45, N 6.86). In Lösung fluoresciert die Verbindung intensiv grün. In wässriger alkoholischer Natronlauge löst sie sich mit tiefroter Farbe, die beim Stehenlassen oder Erwärmen vollständig verschwindet. Nach dem Ansäuern kann man aus dieser Lösung 2-Acetyl-indolyl-3-essigsäure in guter Ausbeute isolieren. Schmp. 214° (Zers.) (Ber. N 6.46; Gef. N 6.52) Mit Acetanhydrid erhält man daraus die gelbe Verbindung zurück.

Nach den Eigenschaften kommt für diese Verbindung nur die Struktur II oder deren polare mesomere Formen IV-VI infrage. Die gelbe Farbe macht eine Beteiligung des einsamen Elektronenpaars am Stickstoff wahrscheinlich; Formel V dürfte am meisten Gewicht haben. U.V.Spektrum (in Äthanol): 245 mμ log ε 4.5; 270 mμ log ε 4.3; 305 mμ log ε 4.0.



I II III

IV V VI

Die gleichen Umsetzungen ließen sich ausgehend von Indolyl-3.4-diessigsäure durchführen. Die erhaltene Verbindung vom Schmp. 260° $C_{14}H_{11}O_4N$ (Ber. C 65.40, H 4.28, N 5.44; Gef. C 65.40, H 3.68, N 5.34) zeigt ebenfalls die starke grüne Fluorescenz. Anscheinend ist diese Reaktion bei allen Indol-3-essigsäure-derivaten durchführbar, die eine freie 2-Stellung aufweisen.

Unterwirft man Indolyl-3-acetamid den gleichen Reaktionsbedingungen, so erhält man eine gelbe Verbindung vom Schmp. 207-210°, die in Lösung ebenfalls grün fluoresciert.

Wir schlagen vor, die Verbindungen als Indolopyrone

und Indolopyridone zu benennen.[1] Die Verbindung II heißt demnach Indolo-(2'.3';4.5)-6-methyl-pyron-(2).

Die chemische und spektroskopische Untersuchung der Verbindungsklasse wird fortgesetzt.

---

1. in Anlehnung an die Benennung der Indolochinoline durch F.G. Mann, A.F. Prior und T.J.Willcox, J.Chem.Soc. 1959, 3803.

Tetrahedron Letters No.11, pp. 18-21, 1960. Pergamon Press Ltd. Printed in Great Britain.

STRUCTURE OF BULNESOL

STEREOCHEMISTRY OF GUAIOL, NEPETALINIC ACIDS AND IRIDOMYRMECINS

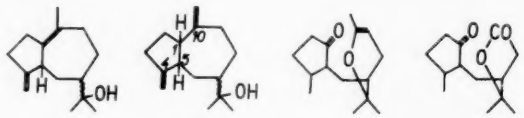
L. Dolejš, A. Mironov* and F. Šorm

Institute of Organic Chemistry and Biochemistry,

Czechoslovak Academy of Science, Prague

(Received 13 April 1960)

ON the basis of the facts presented in this paper, the structure I has been suggested for bulnesol, the sesquiterpenic alcohol $C_{15}H_{26}O$ which accompanies guaiol in guaiac wood oil (Bulnesia sarmienti Lor.).



I II III IV

In view of earlier investigations, bulnesol is a bicyclic tertiary alcohol containing one double bond.[1] On dehydration with thionyl chloride, bulnesol afforded a diene which on subsequent dehydrogenation with sulphur yielded guaiazulene, identified as the adduct with s-trinitrobenzene, m.p. 151°, undepressed on admixture of an authentic sample.

---

* Present address: Institute of Light Organic Technology, Moscow.

[1] H. Wienhaus and H. Scholz, Ber. Schimmel 269 (1929).

1960

The dihydroderivative of bulnesol, m.p. 74-76°, according to the infra-red spectrum, mixed melting point and optical rotation, is identical with the crystalline isomer of dihydroguaiol II.*

On oxidation with chromic acid in acetic acid, dihydrobulnesol afforded products identical with those from dihydroguaiol II. As a neutral material we obtained a ketone of molecular formula $C_{12}H_{20}O$ (Found: C, 80.15; H, 11.11. Calc.: C, 79.94; H, 11.18%), affording a semicarbazone, m.p. 203-208° and $[\alpha]_D^{20}$ -78.6° (AcOH) (Found: C, 65.62; H, 9.74; N, 17.69. $C_{13}H_{23}N_3O$ requires: C, 65.78; H, 9.77; N, 17.71%) and a benzylidene derivative of m.p. 147.5°. The acidic material formed a dicarboxylic acid of molecular formula $C_{12}H_{20}O_4$, m.p. 186-187° (Found: C, 63.14; H, 8.64. Calc.: C, 63.13; H, 8.83%).

Ozonolysis of bulnesol and subsequent hydrogenation of the resulting ozonide on palladized charcoal led to the enol ether III, m.p. 99-100° (Found: C, 76.14; H, 10.26. $C_{15}H_{24}O_2$ requires: C, 76.22; H, 10.24%). Infra-red spectrum of this substance exhibited absorption bands at 1744 cm^{-1} (γ (C = O) in a five-membered ring) and at 1685 cm^{-1} [γ (C = C) in enol ether].[2] Unlike bulnesol, the enol ether showed in its infra-red spectrum no frequencies for a hydroxyl group. The formation of a monosemicarbazone m.p. 174-175° (Found: C, 65.18; H, 9.32; N, 13.98. $C_{16}H_{27}N_3O_2$ requires: C, 65.49; H, 9.28; N, 14.32%) is in agreement with the presence of only one carbonyl group in III. The compound III gave iodoform at Legal test and gave a positive tetranitromethane reaction. The double bond, according to the ultra-violet spectrum, is not conjugated with the keto group. On

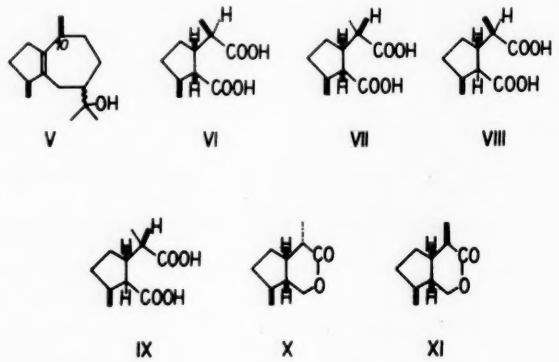
---

* Melting point of dihydroguaiol is 79°. We explain the lower melting point of dihydrobulnesol by the admixture of a stereoisomer.

[2] P. Wieland, K. Hausler, H. Ueberwasser and A. Wettstein, [Helv. Chim. Acta 41, 74 (1958)] found values about 1680 cm^{-1} for steroidal cyclic enol ethers.

ozonolysis and subsequent hydrolysis, the ether III afforded acetic acid, characterized by paper chromatography and by preparation of the p-bromophenacyl ester. The product of ozonolysis when oxidized with potassium permanganate in acetic acid, afforded acidic material from which was prepared a 2,4-dinitrophenylhydrazone, m.p. 173° insoluble in hydrogen carbonate solution (Found: N, 14.07. $C_{19}H_{24}N_4O_6$ requires: N, 13.86%). The sunstance obviously is the hydrazone of the keto-lactone IV. From the results follows the location of the double bond of bulnesol as shown in formula I.

Djerassi et al.[3] inferred for dihydroguaiol the absolute



V VI VII VIII

IX X XI

configuration on carbon atoms C_1, C_4 and C_5.*

On the basis of the identity of dihydrobulnesol and dihydroguaiol, the

---

* We wish to express our gratitude to Professor Djerassi who sent us the manuscript of his paper "On the Absolute Configuration of Guaiol. Correlation with Nepetalinic Acid" before publishing.

3 E.J. Eisenbraun, T. George, B. Riniker and C. Djerassi, J. Amer. Chem. Soc. 82, to be published (1960).

absolute configuration of bulnesol, expressed with formula I, may thus be inferred. Assuming the cis-addition of hydrogen at hydrogenation of bulnesol, we may infer also the obsolute configuration on C_{10} of guaiol and its crystalline dihydroderivative in the sense of structure V and II respectively. From the above follows even the absolute configuration on the side-chain methyl group of four isomeric nepetalinic acids[3] of.4,6; the particular acids possess following structures: the isomer of m.p. 85°: VI, the isomer of m.p. 117°: VII, the isomer of m.p. 115°: VIII and the isomer of m.p. 111°: IX. Iridomyrmecin and isoiridomyrmecin, the relationship of which to nepetalinic acids has been known[4], possess absolute configuration expressed by formulae X and XI, respectively.

---

[4] R.B. Bates, E.J. Eisenbraun and S.M. McElvain, J. Amer. Chem. Soc. 80, 3420 (1958).

[5] S.M. McElvain and E.J. Eisenbraun, J. Amer. Chem. Soc. 77, 1599 (1955).

Tetrahedron Letters No.11, pp.22-24, 1960. Pergamon Press Ltd. Printed in Great Britain.

BOND ALTERNATION IN CYCLOÖCTADECANONAENE (CON)

M. Gouterman and G. Wagniere

Conant Chemical Laboratory, Harvard University, Cambridge 38, Massachusetts

(Received 20 April 1960)

THE molecule CON, which has recently been synthesized by Sondheimer and co-workers,[1] is of great theoretical interest because its spectrum should be exactly predictable. If, as has been supposed, the molecule is fully conjugated,[1,2] the transition energies should be given by the Moffitt[3] theory of cyclic polyenes. According to this theory, which has proven highly successful in the interpretation of polyacene spectra, a cyclic polyene of length $(4\nu + 2)$ should have transitions with energy:

$$\Delta E(\Xi) = 4\beta(\Xi) \sin \phi, \left(\phi = \frac{\pi}{(4\nu + 2)}\right)$$

where the resonance integrals $\beta(\Xi)$ are set to fit the three benzene transitions $\Xi = {}^{E}_{1u}, {}^{B}_{1u}, {}^{B}_{2u}$. This predicts for CON transitions with the same symmetries at 510, 580, and 730 mμ respectively, in striking discord with the reported transitions[1] 378, 415, and 456 mμ. (The band at 378 mμ, with ε roughly 10 times that of the other two bands, is identified with the allowed E_{1u} transition). The failure of a theory that has been so successful in other

---

[1] F. Sondheimer and R. Wolovsky, Tetrahedron Letters No. 3, 3 (1959).

[2] D.W. Davies, Tetrahedron Letters No.8, 4 (1959).

[3] W. Moffitt, J. Chem. Phys. 22, 320 (1954).

cases leads naturally to a reexamination of basic assumptions concerning this molecule.

The assumption that appears most suspect is that of equal bond lengths. It has been found empirically that the bond lengths in linear polyenes continue to alternate even as molecules tend to get very long.[4] Theoretical explanation for this fact was given by Labhart.[5] Further studies by Ooshika[6] and by Longuet-Higgins and Salem[7] indicate that the same behavior should hold in cyclic systems. It therefore seems reasonable to look for bond alternation in CON.*

The Moffitt theory allows for a most convenient calculation of the effect of bond alternation. We shall assume the double bonds are characterized by β_1 and the single bonds by β_2. (That this should send the transitions to shorter wave length may be seen intuitively from the fact that in the extreme limit the molecule appears as 9 ethylenes with $\lambda \sim 1800$ Å.) If one defines $\beta = (\beta_1 + \beta_2)/2$ and $\delta = (\beta_1 - \beta_2)/2$, it may be shown that the transition energy becomes:

$$\Delta E = 4\sqrt{\beta^2 \sin^2\phi + \delta^2 \cos^2\phi},$$

where $\phi = \pi/(4\nu + 2)$, as before. It is, however, no longer clear that the Moffitt procedure of choosing three values of β (Ξ) is justified. If we choose a single value of β=3.14 eV to fit the average of the benzene

* It is a suggestive coincidence that the linear 18-membered polyene absorbs in the very same region as CON. See F. Bohlmann, Ber. 85, 388 (1952).

4 W. Drenth and E.H. Wiebenga, Acta Cryst. 8, 755 (1955).

5 H. Labhart, J. Chem. Phys. 27, 957 (1957).

6 Y. Ooshika, J. Phys. Soc. Japan 12, 1246 (1957).

7 H.C. Longuet-Higgins and L. Salem, Proc. Roy. Soc. A 251, 172 (1959).

levels, it follows that $\delta = 0.175\beta$ will yield $\lambda = 405$ mμ agreeing with the average observed for CON.

The value of δ given above is rather large. In fact, comparison with the β values of butadiene[8] indicates that the alternation in CON is of the same order of magnitude. This would suggest a difference in bond lengths of about 0.1 Å in agreement with Ooshika's prediction of 0.12 Å. The treatment of Longuet-Higgins predicts bond alternation of about 0.04 Å beginning with systems $(4\nu + 2) \approx 34$; however, he points out that this result is very sensitive to details and alternation could begin at $(4\nu + 2) = 18$. The X-ray studies in progress[1] may settle these questions. Meanwhile, further theoretical studies are being carried out at this laboratory.

---

[8] B. Pullman and A. Pullman, Les Théories Electroniques de la Chimie Organique p. 200. Masson et Cie., Paris (1952).

Tetrahedron Letters No.11, pp. 25-26, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

THE STRUCTURE OF ECHITAMINE (ADDENDUM)

(Mrs.) D. Chakravarti, R. N. Chakravarti, (Miss) R. Ghose

School of Tropical Medicine, Calcutta

and

Sir Robert Robinson

(Received 23 April 1960)

A recent letter[1] mentioned work on the chemistry of echitamine undertaken by the three first-named authors since 1955 [thesis (R. Ghose) Calcutta, 1957] and the postulated relationship with pseudo-akuammigine, also dating from before 1957. Our views on the structural aspect were largely in agreement with Conroy et al[2] and differed from those expressed by Govindachari[3], Birch[4] and (Mrs.) A. Chatterjee[5] with their respective collaborators. In particular we rejected formulae [3,4,5] containing $\ddot{N}Me$(a) · $\dot{C}$(OH) in favour of one containing $\ddot{N}Me$(b) · CH(OH) and we also considered that the pseudo-strychnine-like structure[2] should be replaced by one based on the N(b) methylajmaline model.

Further consideration of the evidence presented by Conroy et al and by Chatterjee et al (loci cit), the significance of which we had not fully appreciated, suggests that the MeN(b) · CHOH group may not be in

---

1 The present authors, Tetrahedron Letters No. 10, 10 (1960).

2 H. Conroy, R. Bernasconi, P. R. Brook, R. Ikan, R. Kurtz and K. W. Robinson, Tetrahedron Letters No. 6, 1 (1960).

3 T. R. Govindachari and S. Rajappa, Proc. Chem. Soc. 134 (1959)

4 A. J. Birch, H. F. Hodson and G. F. Smith, Proc. Chem. Soc. 224 (1959)

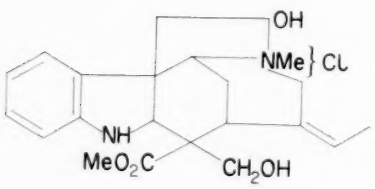
5 A. Chatterjee, S. Ghosal and S. G. Majumdar, Chemistry and Industry 265 (1960).

the same position as in methylajmaline salts but in the alternative position with the original tryptamine side-chain in the form $-CH_2 \cdot CH(OH) \cdot \ddot{N}Me\}$ Cl (echitamine chloride).

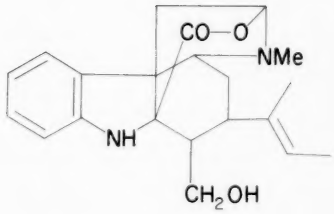
The superiority of this modification follows from the observation of Conroy et al that catalytic reduction of echitamine chloride affords the crystalline base echitinolide, $C_{21}H_{26}O_3N_2$, containing 2 Me(C) groups. This lactone is the result of hydrogenolysis of an allylic group and as the three oxygens are retained, the original salt cannot contain $Me\ddot{N}(b) \cdot CH(OH) \cdot \dot{C} = CHMe$. Therefore the - CH(OH) must be on the other side of N(b) in the group $\cdot CH_2 \cdot CH(OH) \cdot \ddot{N}Me \cdot CH_2 \cdot \dot{C}:CHMe$.

This small but important modification also accommodates the finding of Chatterjee et al.[5] that the oxidation of echitamine with periodic acid affords indole-3-acetaldehyde.

The structure which we now propose for echitamine chloride is (I) and echitinolide would be a lactone with a 7-membered bridge (II).



I



II

Tetrahedron Letters No.11, pp. 27-35, 1960. Pergamon Press Ltd. Printed in Great Britain.

THIOCYANATES AND ISOTHIOCYANATES. EQUILIBRIUM, KINETICS AND MECHANISMS OF ISOMERIZATION

A. Iliceto, A. Fava and U. Mazzucato

Istituti di Chimica della Facolta' di Scienze,

Universita' di Padova, Italy

(Received 26 April 1960)

THIOCYANIC acid esters have long been known to undergo thermal isomerization to give the corresponding isothiocyanic acid esters. Although the isomerization reaction is believed to be quite general and is frequently used as a synthetic route to isothiocyanates, little is known about its nature and mechanism. We wish to report here a number of observations which may have considerable mechanistic significance.

Saturated systems, kinetics

In all cases recorded in the literature,[1] drastic temperature conditions are required to obtain isomerization; this

---

[1] See for istance: [a] A.W.Hofmann, Ber. 13, 1349 (1880); [b] J.Gillis, Rec. Trav. Chim. 39, 330 (1920); [c] E.Schimdt W. Striewsty, M.Seefelder and F.Hitzler, Ann. 568, 192 (1950); [d] H.Hennicke, Ann. 344, 24 (1906); [e] H.L.Wheeler, Amer. Chem. Jour. 26, 345 (1901).

appears to be often accompanied by extensive decomposition. Milder conditions can be adopted, however, in the presence of electrophilic catalysts, such as $ZnCl_2$ or CdI_2.[1b,1c] The catalytic action of electrophilic agents suggests that the isomerization may occur by way of an ionization mechanism. To test this hypothesis, we have investigated a number of systems which, because of the nature of the organic substrate, would be expected to ionize readily. The benzhydryl substrate has been proved ideal in this respect, since the isomerization was found to take place at relatively low temperatures, smoothly and to the exclusion of side reactions. Some representative kinetic results are reported under Table I. The rate of isomerization appears to be considerably accelerated by polar media, by the presence of 'inert' salts and by the introduction of electron releasing substituents in the organic moiety: the latter effect is comparable in magnitude [in methyl ethyl ketone, $\rho \simeq 3{,}5$ (calculated from Brown's σ^+)[2]] to that observed for the solvolysis of benzhydryl chlorides in ethanol ($\rho = 4{,}05$).[2] These

---

[2] Y. Okamoto and H.C. Brown, J. Org. Chem. 22, 485 (1957).

1960

TABLE I

First-order rate coefficients [a] for the isomerization of benzhydryl thiocyanates:

Compound X	Compound X'	Solvent	t° C	10^5 k (sec^{-1})
H	H	MeEtCO	90	2.2
		MeCN	90	32
		MeEtCO + $NaClO_4$ 0.1M	90	6.0
		MeEtCO	50[b]	0.026
CH_3	CH_3		50	7.8
H	H		130[b]	77
NO_2	H		130	0.25

[a] Determined by I.R. spectrophotometry.

[b] Extrapolated from data taken between 70° and 90°.

effects point consistently towards a rate determining ionization. Whether ionization involves dissociation, or stops to

some kind of ion-pair,[3] the results cannot tell. Experiments of exchange and simultaneous isomerization which are now under way, will clarify this point. Whatever the detailed mechanism may be, it appears likely that an ionization mechanism is applicable for most saturated systems.

Allylic systems, kinetics

Allylic thiocyanates appear to isomerize at much faster rates than other systems (e.g. benzyl) of comparable electron releasing ability. This behaviour is attributed to the allylic structure providing a path to isomerization through an intramolecular rearrangement. The correctness of this view was proved in 1940 by Mumm and Richter[4] who showed that, upon heating, crotyl thiocyanate is converted to α-methylallyl isothiocyanate:

$$CH_3CH{=}CHCH_2SCN \longrightarrow CH_3CH(NCS)CH{=}CH_2$$

and more recently by us[5] for γ,γ-dimethylallyl thiocyanate. Although these are the only mechanistic studies so far performed, an intramolecular mechanism is believed to hold for most allylic

---

3 S. Winstein, E. Clippinger, A.H. Fainberg, R. Heck and G.C. Robinson, J. Amer. Chem. Soc. 78, 328 (1956).

4 O. Mumm and H. Richter, Ber. 73, 483 (1940).

5 Unpublished results.

thiocyanates.[6] However, with no kinetic data at hand, the details of the mechanism remained obscure. The kinetic results summarized in Table II allow a better particularization of the

TABLE II

First-order rate coefficients[a] at 60° for the isomeric rearrangement of allylic thiocyanates:

$$RR'C{=}CHCH_2SCN \longrightarrow RR'C(NCS)C{=}CH_2$$

Compound		$10^5\ k_{60°}(sec^{-1})$		$(k_A/k_C)_{60°}$
R	R'	A[b]	C[b]	
H	H	1.8	3.3	0.5
CH_3[c]	H	27	31	0.9
CH_3	CH_3	270[d]	96[d]	3

[a] Determined by U.V. spectrophotometry.

[b] A and C stand for acetonitrile and cyclohexane solver respectively.

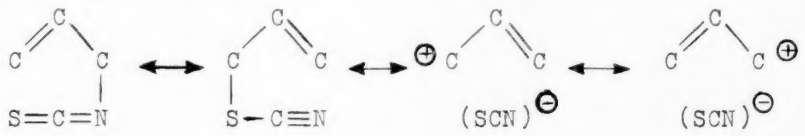
[c] trans

[d] Extrapolated from lower temperature data.

[6] R. H. DeWolfe and W. G. Young, Chem. Rev. 56, 856 (1956).

intramolecular mechanism. Most helpful to this end, is the combined consideration of solvent and structure effects. As shown, the rate of isomerization increases in the sequence: allyl $<$ γ-methylallyl $<$ γ,γ-dimethylallyl, the variation being more pronounced in the more polar solvent. Thus, the reaction appears to be favored by electron releasing substituents, the more so in the more polar solvent. Moreover, it is interesting to remark that, while for allyl and γ-methylallyl thiocyanates the reaction is faster in cyclohexane than in acetonitrile, the reverse is true for γ,γ-dimethylallyl thiocyanate. In any case, it has to be noted that, considering the wide polarity difference of the solvents concerned, these medium effects are quite small.

In agreement with the above evidence, it appears that a satisfactory representation of the transition state can be given in terms of the following structures:



I II III IV

This description is essentially that given by Young, Winstein

and Goering[7] for the rearrangement of α,α-dimethylallyl chloride. The main distinction between that rearrangement and the present ones, lies in the different weight carried by the ionic structures, III and IV, with respect to the purely covalent ones, I and II. In the present example, the smallness of the structure and solvent effects[8] and especially the direction of the latter for the first two members, strongly indicate that the bonding in the transition state is largely, though not wholly, covalent.

Equilibrium

The reverse change, isothiocyanate to thiocyanate has never been clearly established. We have now found evidence that in the isomerization of thiocyanates an equilibrium is reached in which substantial amounts of thiocyanate may be present.

Some representative results are collected in Table III.

---

7 W.G. Young, S. Winstein and H.L. Goering, J. Amer. Chem.Soc. 73, 1958 (1951).

8 At first sight these effects may not seem to be small. However, in the reactions of allylic systems which occur by way of an ionization mechanism, much larger solvent and structure effects are observed. For a summary of data, see A. Streitweiser, Jr., Chem. Rev. 56, 650 (1956).

TABLE III

Equilibrium thiocyanate/isothiocyanate at 100° in different media.

Compound	% of thiocyanate at equilibrium[a]			Conc. m/l
	Pure	cyclo-hexane	aceto-nitrile	
Benzhydryl	-	<1	2-3	0.1-0.75
allyl	<1	<1	9-11 (3)[b]	10^{-3} - 10^{-1}
γ-methyl-allyl	11	5	27	10^{-3}
γ,γ-dimethyl-allyl	40	18	50	10^{-3}

[a] Analysis by U.V. and I.R. spectrophotometry.

[b] In methyl ethyl ketone.

As shown, either in the pure state or in non polar solvents, the fraction of thiocyanate at equilibrium is generally too small to be detected, while it becomes appreciable in polar

media such as acetonitrile or methyl ethyl ketone. This behaviour is consistent with the greater dipole moment of thiocyanates, which consequently become stabilized in such media.

The equilibrium may be pushed further to the thiocyanate side whenever the isomerization proceeds by way of a molecular rearrangement which produces a less stable carbon skeleton. This appear to be the case of γ-methyl substituted allylic thiocyanates for which, in the isomeric rearrangement, there is loss of hyperconjugation energy due to the isolation of the double bond from the methyl group(s). In this connection, the observed[9] failure of γ-phenylallyl thiocyanate to undergo isomeric rearrangement can be conveniently explained on equilibrium grounds. In fact, due to the conjugation of the allylic double bond with the phenyl ring, γ-phenylallyl thiocyanate may be stabilized, with respect to α-phenylallyl isothiocyanate, to the point that, at equilibrium, the latter is not even detectable. This viewpoint is further substantiated by the fact that, in the attempted preparation of α-phenylallyl isothiocyanate from α-phenylallyl amine and carbon disulphide, the only product which could be isolated was γ-phenylallyl thiocyanate.[10]

---

[9] E. Bergmann, J. Chem. Soc. 1935, 1361.

[10] A. Iliceto and G. Gaggia, Gazz. Chim. Ital. 90, 262 (1960).

Tetrahedron Letters No. 12, pp.1-4, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

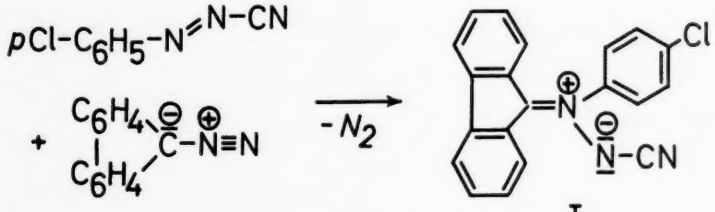
AZOMETHIN-IMINE, EINE NEUE KLASSE ZWITTERIONISCHER VERBINDUNGEN

Rolf Huisgen, Rudolf Fleischmann und Albrecht Eckell

Institut für Organische Chemie der Universität München

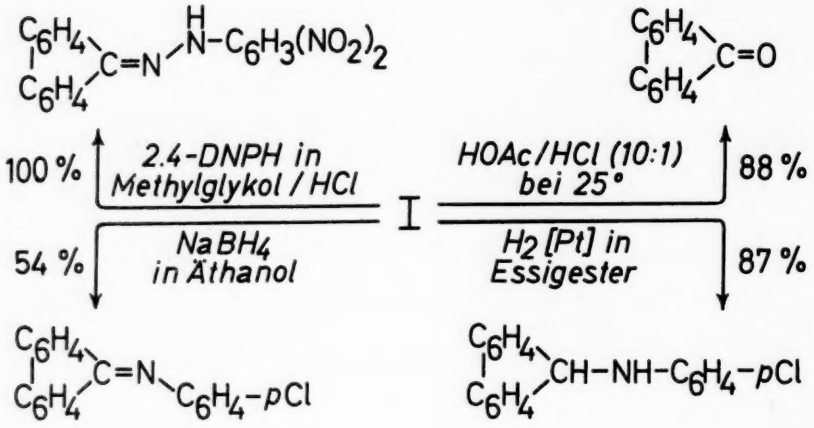
(Received 9 May 1960)

VEREINIGT man äquimolare Mengen anti-p-Chlorbenzol-diazocyanid und Diazofluoren in Äthylenchlorid oder Aceton bei 20°, dann wird unter leichter Selbsterwärmung ein Moläquiv. N_2 freigesetzt; leuchtend orangerote Kristalle mit Schmp. 192-193° u.Z., die in Analyse und Molekulargewicht der Formel $C_{20}H_{12}N_3Cl$ entsprechen, werden zu 93% d.Th. isoliert.

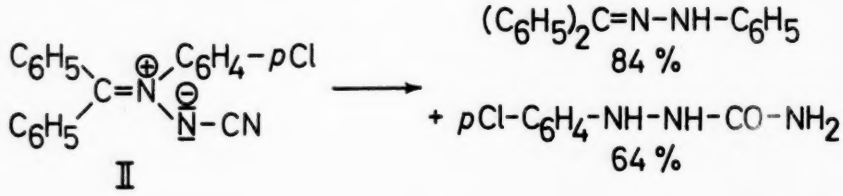


I

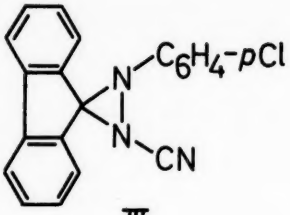
Die Reduktionen und Spaltungen an der CN-Bindung stehen im Einklang mit Formel I:



Analoge Verbindungen gehen aus dem elektrophilen Angriff von p-Brombenzol- und p-Nitrobenzol-diazocyanid auf Diazofluoren in 90% bzw. 85% Ausbeute hervor (Schmp. 195-197° u.Z. bzw. 209° u.Z.). Mit Diphenyl-diazomethan liefern die drei aromat. Diazocyanide entsprechende Azomethin-imine der Benzophenon-Reihe zu 81-89% d.Th.. Für die Konstitution II des Produktes aus p-Chlorbenzol-diazocyanid und Diphenyl-diazomethan spricht vor allem die Umsetzung mit Phenylhydrazin in Alkohol/Wasser/Schwefelsäure bei 20°:



Die chemischen Befunde gestatten keine eindeutige Unterscheidung zwischen den offenkettigen, zwitterionischen Strukturen und Derivaten des Diaziridins, etwa III anstelle von I.



III

Tatsächlich werden die Reaktionsprodukte des Azodicarbonsäureesters mit Diazoalkanen als Diaziridine formuliert.[1]

Ein entscheidendes Argument zugunsten der offenen Azomethin-imin-Formel bieten die Elektronen- und Schwingungsspektren. I und II verfügen über fließend-konjugierte Systeme, während in III die chromophoren Bezirke durch das zentrale, tetraedrische Kohlenstoffatom isoliert sind. I besitzt eine starke Absorptionsbande im Sichtbaren mit λ_{max} = 434 mμ (log ε = 4.43). Auch der Einfluß von Kernsubstituenten auf das Spektrum von II entspricht der Erwartung für das Zwitterion.

Die infrarote Nitrilschwingung ist mit 4.73μ für I und 4.70μ für II ungewöhnlich langwellig. Nur für Cyanamid-Anionen findet sie sich in diesem Bereich: $(C_6H_5\text{-}\overset{\ominus}{N}\text{-}CN)Na^{\oplus}$ 4.76μ, $(pNO_2\text{-}C_6H_4\text{-}\overset{\ominus}{N}\text{-}CN)Na^{\oplus}$ 4.72μ. In den freien Aryl-cyanamiden liegt die Bande bei 4.52μ.

Die hier erstmalig beschriebenen Azomethin-imine sind die Imin-Analogen der Azomethin-oxyde, die unter dem Namen Nitrone

---

[1] E.Müller, Ber.Dtsch.Chem.Ges. 47, 3001 (1914); H.Staudinger und A.Gaule, Ibid. 49, 1961 (1916); O.Diels und H.König, Ibid. 71, 1179 (1938); F.Jakob, Diplomarbeit Univ.München 1953.

bekannt sind. Die geringe Neigung der Zwitterionen I und II zur 1.3-Addition nucleophiler Verbindungen HX äußert sich in der Stabilität gegenüber Alkohol und kaltem Anilin; Anilin bei 100° überführt II in Benzophenon-anil.

Der Deutschen Forschungsgemeinschaft und dem Fonds der Chemischen Industrie sei für die freundl. Förderung dieser und der beiden folgenden Arbeiten gedankt.

Tetrahedron Letters No.12, pp.5-8, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

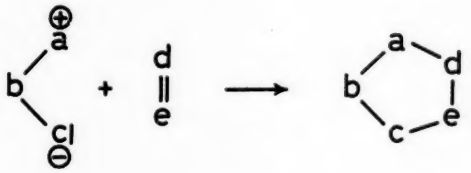
1.3-DIPOLARE ADDITIONEN DER AZOMETHIN-IMINE

Rolf Huisgen und Albrecht Eckell

Institut für Organische Chemie der Universität München

(Received 9 May 1960)

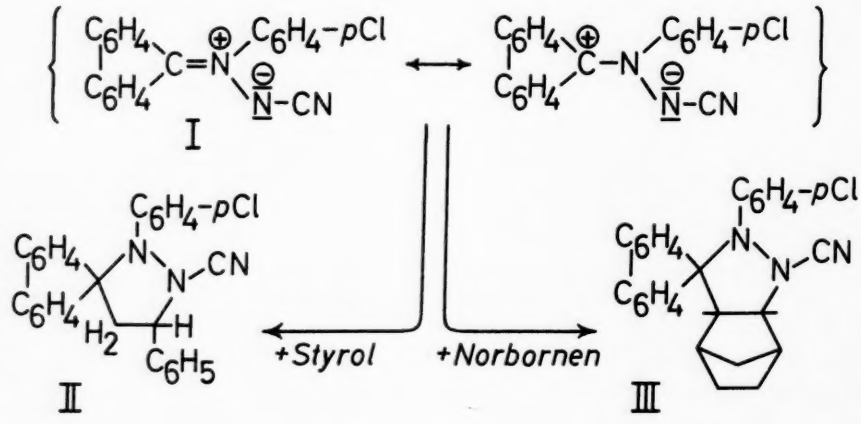
IN den Jahren 1958-1960 wurde in unserem Laboratorium die Anlagerung von 1.3-Dipolen an Mehrfachbindungssysteme, die sog. Dipolarophilen, als in weiten Grenzen verallgemeinerbare Reaktion erkannt. Zahlreiche Zwitterionen, die in 1.3-Stellung ein Elektronensextett mit positiver Ladung und am negativen Ladungszentrum ein freies Elektronenpaar besitzen, sind dieser "1.3-Dipolaren Addition" unter Bildung 5-gliedriger Ringsysteme zugänglich.[1]



[1] R.Huisgen, Vortrag "Theoretische Chemie und Organische Synthese"; Festschrift der Zehnjahresfeier des Fonds der Chemischen Industrie, Düsseldorf 1960.

Die Azomethin-ylide, -imine und -oxyde gehören zu den Systemen, die in der Schreibweise als 1.3-Dipol keine Doppelbindung mehr besitzen. Alle drei Azomethinium-betaine sind zu Cycloadditionen befähigt; die des Imins und Oxyds seien hier und in der folgenden Mitteilung kurz beschrieben.

Erwärmt man das orangerote Azomethin-imin I [2] mit überschüssigem Styrol auf 70°, so gelangt man in 92% Ausbeute zum farbl. 1:1-Addukt II (Schmp. 183-184° u.Z.), wie Analyse und Molekulargewicht zeigen. Die Bildung eines Norbornen-Addukts III zu 90% d.Th. zeugt von der Additionsfreudigkeit der gespannten Doppelbindung; analoge farbl. Addukte liefern z.B. Dicyclopentadien (47%), Norbornadien (79%) und Bicyclo-[2.2.1]-hepten-(2)-nitril-(5) (91%).



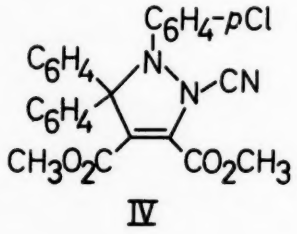
[2] R.Huisgen, R.Fleischmann und A.Eckell, Tetrahedron Letters No. 12, 1 (1960).

Die Fähigkeit α,β-ungesättigter Carbonylverbindungen und Nitrile zur Vereinigung mit I bei 80-90° sei mit folgenden Beispielen illustriert:

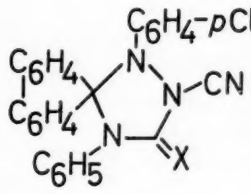
Acrylsäure-äthylester	85%	Addukt, Schmp.u.Z.	124-125°
Maleinsäure-dimethylester	66%	" "	176-177°
p-Nitro-zimtsäure-äthylester	76%	" "	156-158°
Acrylnitril	83%	" "	176°

Diese Additionen zu Pyrazolidinen erfolgen so glatt, daß man an die analytische Verwendung der Azomethin-imine zur Charakterisierung flüssiger Olefine denken kann; isolierte Doppelbindungen treten allerdings schwerer in Reaktion.

Auch die Acetylenbindung ist dipolarophil. Farbl., kristalline Addukte von I werden mit Acetylen (Schmp. 151-152°), Phenylacetylen (75%, Schmp. 172°), Tolan (28%, Schmp. 202-203° u.Z.), 1-Hexin (35%, Schmp. 196-197°) und Propinal-dimethylacetal (67%, Schmp. 168°) bei 60-80° erhalten. Acetylen-dicarbonsäure-dimethylester gibt schon bei Raumtemp. 93% d.Th. des bei 98-100° schmelzenden Δ^3-Pyrazolins IV.



IV



V, X = O
VI, X = S

Als besonders aktive Dipolarophile liefern Phenyl-isocyanat und Phenylsenföl die reinen Addukte V (Schmp. 172-173° u.Z.) in 75 bzw. 86% Ausbeute.

Andere Azomethin-imine [2] gehen analoge 1.3-Dipolare Additionen ein. Die spektralen Änderungen bei der Adduktbildung befinden sich im Einklang mit den Pyrazolidin-, Pyrazolin- und Triazolidin-Formeln. Der langwelligen Nitrilschwingung von I [2] entspricht in den Addukten eine normale Cyanamid-Bande bei 4.45-4.55μ. Eine kräftige Bande bei 6.48-6.52μ, die in allen Addukten verschwindet, ist wohl der CN-Doppelbindung der Azomethin-imine zuzuschreiben. Mit der konstitutionellen Sicherung der Addukte durch Abbau sind wir beschäftigt. Die in II und V gewählte Additionsrichtung gründet sich auf die analogen, strukturell geklärten Nitron-Addukte.[3] Über weitere Typen von Azomethin-iminen und deren Cycloadditionen wird an anderer Stelle berichtet.[4]

---

[3] R.Grashey, R.Huisgen und H.Leitermann, Tetrahedron Letters No. 12,9 (1960).

[4] R.Huisgen, R.Grashey, P.Laur und H.Leitermann, Angew. Chem., im Druck.

Tetrahedron Letters No.12, pp. 9-13, 1960. Pergamon Press Ltd. Printed in Great Britain.

1.3-DIPOLARE ADDITIONEN DER NITRONE

Rudolf Grashey, Rolf Huisgen und Herta Leitermann

Institut für Organische Chemie der Universität München

(Received 9 May 1960)

DIE Azomethin-oxyde oder Nitrone sind eine vielbearbeitete Verbindungsklasse, deren vorzügliche Eignung zur 1.3-Dipolaren Cycloaddition [1] überraschend spät erkannt wurde. Einzig die Anlagerung an die NC-Doppelbindung des Phenyl-isocyanats fand sich beschrieben.[2] Jüngst wurde über die intramolekulare Stabilisierung zweier ungesättigter Nitrone zu bicyclischen Isoxazolidinen berichtet.[3] Die ersten Nitron-Additionen an Alkene wurden von M.A.T.Rogers und K.Marsden ausgeführt.[4] Wir studieren seit 2 Jahren 1.3-Dipolare Additionen der Nitrone; mit der Darstellung von mehr als 50 Addukten haben wir den Gültigkeitsbereich der Wechselwirkung mit Olefinen abgesteckt.

---

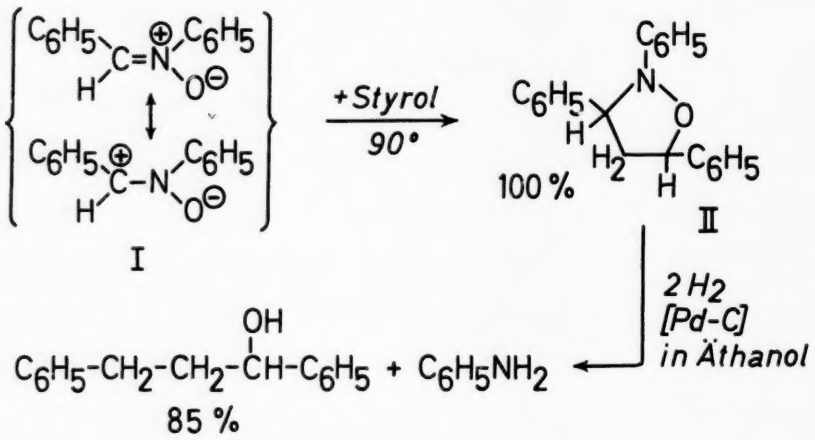
[1] Vgl. R.Huisgen und A.Eckell, Tetrahedron Letters No. 12, 5 (1960).

[2] E.Beckmann, Ber.Dtsch.Chem.Ges. 27, 1957 (1894).

[3] N.A.LeBel und J.J.Whang, J.Amer.Chem.Soc. 81, 6334 (1959).

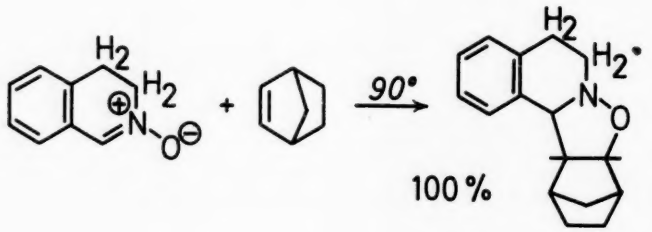
[4] Unveröffentlicht. Wir danken Herrn Dr.M.A.T.Rogers, London, für die freundl. Information im Mai 1958, daß er Piperidein-oxyd an Butadien, Cyclopentadien, Dicyclopentadien und Cyclohexen addiert habe.

Nach 15-stdg. Erwärmen von Diphenyl-nitron (I) mit überschüssigem Styrol auf 85° isoliert man eine quantitative Ausbeute vom 2.3.5-Triphenyl-isoxazolidin (II). Die Hydrogenolyse beweist die Konstitution.

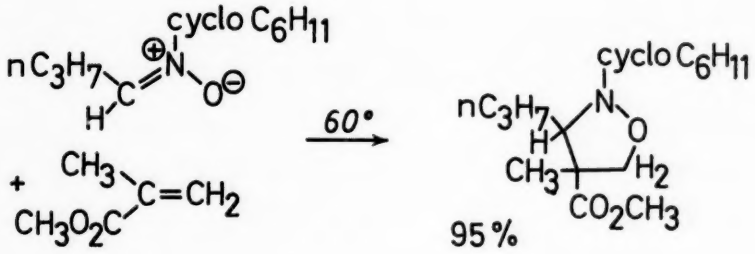


Andere phenylkonjugierte Alkene sowie 1.3-Diene reagieren gleichartig.

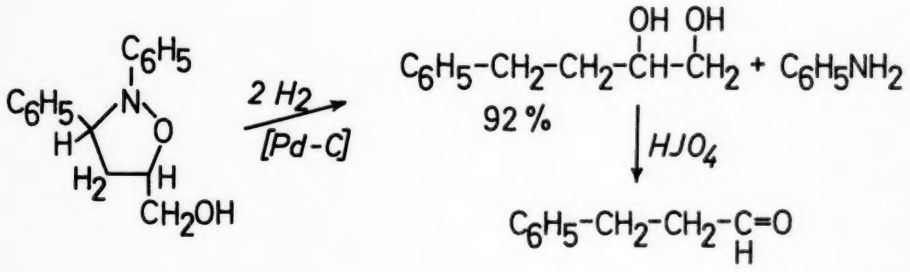
Die Anlagerung der Nitrone an Bicyclo-[2.2.1]-hepten-(2) und Derivate profitiert von der Lösung der Spannungsenergie [5] dieser Doppelbindung. Als Beispiel sei hier ein aliphatisch-aromatisches Nitron gewählt, das 3.4-Dihydroisochinolin-oxyd:



Noch aktivere Dipolarophile (vgl.[1]) sind die α,β-ungesättigten Carbonester, Ketone und Nitrile, die sich zum Teil schon bei Raumtemperatur mit Nitronen vereinigen. Die Addition eines rein aliphatischen Nitrons an Methacrylester sei formuliert; die Additionsrichtung bedarf noch der Sicherung.



Isolierte, gewöhnliche Doppelbindungen sind wesentlich reaktionsträger. Immerhin addiert sich Allylalkohol beim 90-stdg. Erhitzen auf 70° praktisch vollständig an Diphenyl-nitron (99% Addukt). Die Additionsrichtung ist eindeutig:

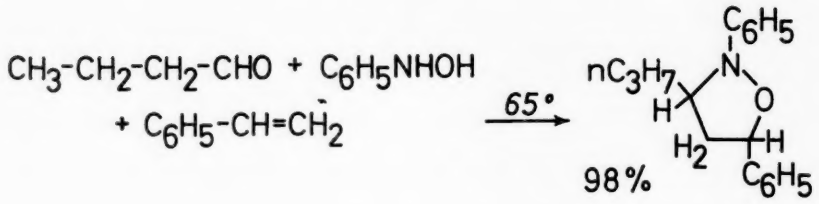


Die Bereitung der Nitrone in situ bietet besonders bei labilen und wenig kristallisationsfreudigen Vertretern Vorteile.[6]

---

[5] R.B.Turner, W.R.Meador und R.E.Winkler, J.Amer.chem.Soc. 79, 4116 (1957).

[6] Auch M.A.T.Rogers bediente sich laut Privatmitteilung (Sept.1959) dieser Methode.



Die nachstehende Tabelle der 1.3-Addukte des C-Phenyl-N-methyl-nitrons wirft die Frage nach der Aktivitätsfolge der dipolarophilen Alkene auf. Ohne die Resultate quantitativer Konkurrenzversuche [7] vorwegzunehmen, sei auf verschiedene, die 1.3-Dipolare Addition begünstigende Faktoren hingewiesen: Energieniveau des Alkens (Spannung), hohe Polarisierbarkeit der Doppelbindung, Stabilisierung von Partialladungen im Übergangszustand der Synchron-Addition.

---

[7] Versuche von Dr.J.A.Craven in unserem Laboratorium.

1960

Tabelle. 1.3-Additionen des C-Phenyl-N-methylnitrons an Alkene; Ausbeuten in % d.Th.

Gespannte Doppelbindungen			
Norbornen	100%	Norbornadien	98%
2.5-Endomethylen-1.2.5.6-tetrahydrobenzonitril			50
3.6-Endomethylen-1.2.3.6-tetrahydrophthalester			30
3.6-Endomethylen-1.2.3.6-tetrahydropyridazin-dicarbonsäure-diäthylester			88
Konjugierte Doppelbindungen			
Cycloheptatrien	83	α-Methyl-styrol	85
Styrol	95	Inden	92
1.2-Dihydronaphthalin	97	1.1-Diphenyl-äthylen	39
α,β-Ungesättigte Carbonester, Ketone, Nitrile			
Äthyl-acrylat	99	Carvon	85
Äthyl-crotonat	95	Eucarvon	68
Acrylnitril	91	Mesityloxyd	53
Maleinsäure-dimethylester			90
Kumulierte Systeme			
Phenyl-isocyanat	94	Phenyl-senföl	53
Gewöhnliche Alkene			
Cyclopenten	90	Allylalkohol	99
Cyclohexen	78	Dihydropyran	

Tetrahedron Letters No.12, pp. 14-17, 1960. Pergamon Press Ltd. Printed in Great Britain.

A RIGOROUS PROOF OF THE SELAGINE STRUCTURE

H. Yoshimura[1], Z. Valenta and K. Wiesner

Organic Chemistry Laboratory, University of New Brunswick
Fredericton, Canada

(Received 9 May 1960)

THE elucidation of the structure of annotinine, the alkaloid of *Lycopodium annotinum* [2], revealed for the first time the structural type to be expected in other *Lycopodium* alkaloids. The key factor in the deduction of this structure was the identification of dehydrogenation products, and extensive systematic degradation[3]. Since then, structures have been proposed for additional alkaloids of this type, namely, lycopodine[4], selagine[5] and the obscurines[6]. Extensive use of N.M.R. spectroscopy[5], dehydrogenation[4,6]

---

[1] N.R.C. postdoctoral fellow on leave from Kyushu University, Japan.

[2] K. Wiesner, Z. Valenta, W.A. Ayer and C. Bankiewicz, *Chem. and Ind.* 1019 (1956); K. Wiesner, W.A. Ayer, L.R. Fowler and Z. Valenta, *Chem. and Ind.* 564 (1957); K. Wiesner, Z. Valenta, W.A. Ayer, L.R. Fowler and J.E. Francis, *Tetrahedron* 4, 87 (1958).

[3] A complete X-ray analysis (M. Przybylska and F.R. Ahmed, *Acta Cryst.* 11, 718 (1958)) corroborated the the proposed structure.

[4] D.B. McLean and W.A. Harrison, in the press.

[5] Z. Valenta, H. Yoshimura, E.F. Rogers, M. Ternbah and K. Wiesner, *Tetrahedron Letters* No.10, 26 (1960).

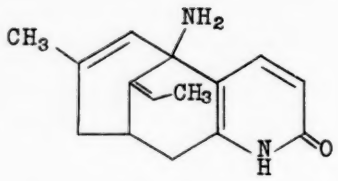
[6] W.A. Ayer and G.G. Iverach, *Tetrahedron Letters* No. 10, 19 (1960).

and skeletal similarities within the Lycopodium group[4,6] were mainly responsible for these structure elucidations.

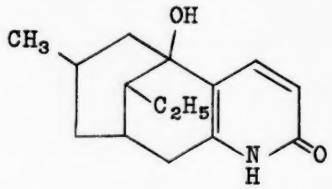
In no case so far reported was it possible to degrade one of the Lycopodium alkaloids in a series of simple (unrearranging) and predictable steps to a known compound. This has now been achieved with tetrahydroselaginol (II), a simple derivative of selagine (I)[5]. Compound II (8.5 mmols) was oxidized in an aqueous $NaOH-K_2CO_3$ solution with $NaIO_4$ (102 mmols)-$KMnO_4$ (5 mmols) for 6 hours at room temperature[7]. The chromatography of the mixture of acidic products on silicic acid yielded several crystalline fractions as a 10% ether in benzene eluate. Repeated crystallization from benzene-petroleum ether gave a keto acid, m.p. 135-139° (Found: C, 64.55; H, 8.95; O, 26.63; C-CH_3, 13.3. $C_{10}H_{16}O_3$ requires C, 65.20; H, 8.74; O, 26.06; 2 C-CH_3, 16.3), IR max ($CHCl_3$) 1709 cm^{-1}, IR max (KBr) 1732 and 1682 cm^{-1}. It was further characterized as a 2,4-dinitrophenylhydrazone, m.p. 212-214° (Found: C, 53.15; H, 5.73. $C_{16}H_{20}O_6N_4$ requires C, 52.74; H, 5.53).

---

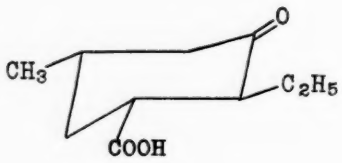
[7] R.U. Lemieux, E. von Rudloff, Can. J. Chem. 33, 1701 (1955).



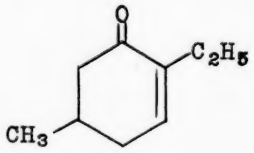
I



II



III



IV

On the basis of the tetrahydroselaginol structure (II), the oxidation product was expected to be 2-ethyl-3-carboxy-5-methyl-cyclohexanone (III).[8] This was confirmed by the following synthesis. The racemic cyclohexenone IV, described previously by Wallach[9], was prepared by the procedure of Nazarov et al.[10] from 2-ethyl-5-methylcyclohexanone[11]. Reflux of IV with KCN in methanol for 4

---

[8] The compound could be expected to be equilibrated at the two epimerizable carbon atoms during the basic reaction and the acidic work-up.

[9] O. Wallach, Ann. 397, 181 (1913).

[10] I.N. Nazarov, L.D. Bergel'son, I.V. Torgov and S.N. Ananchenko, Izvest. Akad. Nauk SSSR., Otdel. Khim. Nauk 1953, 889.

[11] A. Kotz, A.Bieber and A.Schwarz, Ann. 357,192 (1907).

hours[12], followed by hydrolysis with boiling conc. HCl for 3 hours, yielded acid III, m.p. 120-123° (Found: C, 65.15; H, 8.59; O, 26.09). Its infrared spectrum in chloroform solution was superimposable with the spectrum of the degradation product. A mixture of the two acids melted at 120-132°. Clearly, the synthetic product is the racemate of the all-equatorial acid III, while the degradation product is one of its enantiomers.

It should be noted that the keto acid III contains all but 5 carbon atoms of the selagine molecule and that its two oxygen functions clearly reveal the double attachment of the α-pyridone ring to the six-membered carboxylic ring. The placement of the two isolated double-bonds into the completely elaborated selagine skeleton presents no difficulties[5].

---

[12] E. Adlerová, L. Novák and M. Protiva, Chem. Listy 51, 553 (1957).

Tetrahedron Letters No.12, pp. 18-22, 1960. Pergamon Press Ltd. Printed in Great Britain.

DIRECT NUCLEOPHILIC SUBSTITUTION IN HOMOLOGOUS SERIES. TRANSMISSION OF POLAR EFFECTS ALONG A HYDROCARBON CHAIN

A. Fava and A. Iliceto*

Istituto Chimico, Universita' di Camerino, Italy

(Received 28 March 1960; in revised form 2 May 1960)

IN direct nucleophilic substitution reactions at the saturated carbon atom in homologous series $[R(CH_2)_{\underline{n}}X + Y^-]$, an alternation of rates has long been noticed with increasing the length of the hydrocarbon chain. For instance, the effect is observed for direct substitutions (chlorine for iodine) in series such as $Ph(CH_2)_{\underline{n}}X$ and $PhCO(CH_2)_{\underline{n}}X$ and others, where the rate is invariably found to be a maximum for $\underline{n} = 1$, to decrease for $\underline{n} = 2$ and again increase for $\underline{n} = 3$. Where available, e.g. in the $Ph(CH_2)_{\underline{n}}X$ series, the data seem to indicate a zigzagging of rates up to the highest members ($\underline{n} = 7$). In discussing such an effect, Eliel[1] refers to a hypothesis[2] according to which the increased rate for the $PhCO(CH_2)_{\underline{n}}X$ series, and the alternation of rates, could be ascribed to a cyclic transition state of

---

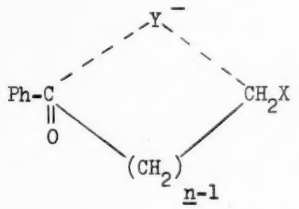
* Istituto di Chimica Organica dell'Universita', Centro di Chimica Nucleare del C.N.R., Padova, Italy.

[1] E.L. Eliel, Steric Effects in Organic Chemistry (Edited by M.S. Newman) pp. 138-140. John Wiley, New York (1956); to which the reader should refer for a summary of data.

[2] E.N. Trachtenberg, Thesis; Harvard University (1952).

1960

type



whose stability would depend on n in relation to the size of the ring formed.[3] Eliel suggests also that a similar explanation may apply to the series $Ph(CH_2)_nX$. The hypothesis is equivalent to assuming some kind of electrophilic assistance by the phenyl ring to the entering (and leaving) group. This is analogous formally at least, to the nucleophilic assistance provided by phenyl groups in solvolysis of ω-phenyl-1-alkyl-benzenesulfonates (anchimeric assistance), for which a definite dependence on n has been recently established.[4]

A way to check the validity of this hypothesis is offered by the study of the kinetic substituent effect. Let us consider, for instance, the series $Ph(CH_2)_nX$ and the rate effects consequent to substitution, say in the 4-position of the phenyl ring, as measured by the reaction constant (ρ of the Hammett equation). If in the transition state there is no assistance by the phenyl group, the substituent effect will simply arise from an inductive effect transmitted along the hydrocarbon chain; the outcome would be a steady decrease of ρ with increasing n (without prejudice of the sign

---

[3] Actually, convincing evidence has been provided [P.D. Bartlett and E.N. Trachtenberg, J. Amer. Chem. Soc. 80, 5808 (1958)] that the enhanced S_N2 reactivity of phenacyl compounds (i.e. n = 1) can be accounted for by a transition state of this kind.

[4] R. Heck, and S. Winstein, J. Amer. Chem. Soc. 79, 3105 (1957); E.J. Corey and C.K. Sauers, Ibid. 79, 248 (1957).

of ρ). If,however, there is phenyl group participation at the transition state, the overall substituent effect would arise from the superimposition, onto the inductive effect transmitted along the chain, of a field effect acting directly at the center of reaction. The latter effect would by-pass the hydrocarbon chain and operate at all n values, its magnitude being determined by the steric requirements of the cyclic transition state. Actually, if this effect were to predominate (i.e. in the case of large phenyl group participation), while ρ should be positive, a parallelism between rate and substituent effect should also be observed.

Data are presented here showing that in the phenylalkyl series the cyclic transition state hypothesis in unlikely. The data concern the rates of substitution (iodine for radioiodine) in the series $Ph(CH_2)_nI$ and its corresponding 4-NO_2 substituted series (n 1 to 5). The relevant results are summarized in Table 1.

It is observed that ρ decreases monotonically from n = 1 to n = 5 without showing any tendency to parallel the rate trend. This indicates that the extent of phenyl group participation, if any, must be very small, since it is insufficient to invert the trend imposed by the weakening inductive effect.

A stronger argument[5] against the cyclic transition state hypothesis is offered, however, by the consideration of $\Delta\rho/\Delta_n$ (last column in Table 1): It is observed that, while ρ decreases only slightly from n = 1 to n = 2, the largest drop occurs for n = 3. This is exactly opposite to what should obtain, were the alternation of rate due to a phenyl group participation which is at a minimum for n = 2 and at a maximum for n = 3. The conclusion

[5] This has been suggested by a referee, whose contribution is gratefully acknowledged.

TABLE 1.

Relative rates of substitution (R-I + $Na^{131}I$) in acetone at 25° [a]

n	$C_6H_5(CH_2)_nI$	$p\text{-}NO_2C_6H_4(CH_2)_nI$	k_{NO_2}/k_H	ρ [b]	$\Delta\rho$
	k_n/k_2	k_n/k_2			
1	484	658	4.73	0.87	0.17
2	1.00	1.00	3.49	0.70	0.36
3	2.46	1.28	1.82	0.34	0.07
4	1.90	0.89	1.64	0.27	0.10
5	2.06	0.80	1.37	0.17	

[a] Second-order rate coefficient for $Ph(CH_2)_2I$:

$k = (2.45 \pm 0.06) \times 10^{-2}$ sec^{-1} l. mole^{-1}

[b] $\rho = \dfrac{\log k_{NO_2}/k_H}{\sigma_p\text{-}NO_2}$, $\sigma_p\text{-}NO_2 = 0.778$

is that, in the phenylalkyl series, the hypothesis of a cyclic transition state does not apply.

As to an alternative explanation of the so-called alternation effect, while it is doubtful that such an effect really exists for the higher members of homologous series, the observed rate sequence could arise, for the first members, from a combination of inductive and steric hindrance effects: While the rate-enhancing inductive effect of the ω-phenyl group progressively weakens with increasing n, steric hindrance goes through a maximum for n = 2, i.e. when the bulky phenyl group is β to the seat of substitution.[6] For

[6] P. Beltrame, L. Oleari and M. Simonetta, Gazz.Chim.Ital. 89, 2039 (1959).

$\underline{n}$ = 3. steric hindrance might be reduced to the point that, in spite of the diminished inductive effect, an over-all rate increase obtains.

Tetrahedron Letters No.12, pp. 23-26, 1960. Pergamon Press Ltd. Printed in Great Britain.

THE TOTAL SYNTHESIS OF 8-ISOTESTOSTERONE

D.K.Banerjee, Vincent Paul and S.K.Balasubramanian

Department of Organic Chemistry, Indian Institute of Science
Bangalore

1960

(Received 11 May 1960)

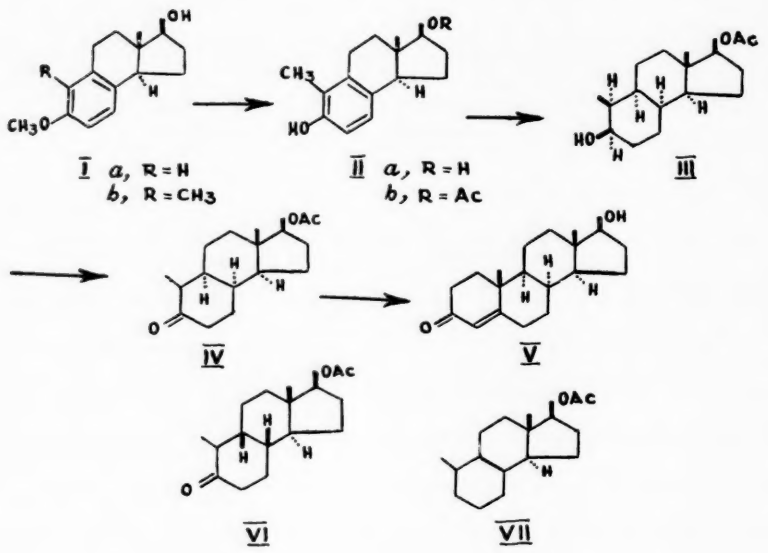
IN 1956, we reported the stereospecific syntheses of the benzohydrindanes (Ia and Ib) and dl-equilenin methyl ether,[1] with the expressed intention of converting Ia and Ib, *via* Birch reduction, to steroids, obviously, by the addition of ring A.[2] Recently Velluz and his coworkers have published a series of papers, wherein they have described the conversion of Ia and one of its optical antipodes to 19-nortestosterone,[3a] cortisone,[3b] and oestradiol[3c] by the method broadly indicated by us, the starting material having been prepared by our method.[1a] In view of these publications,[3] we wish to report the completion of one part of our work in this field, *viz.* the total synthesis of 8-isotestosterone starting from Ib.

---

[1] a. D.K.Banerjee, S.Chatterjee, C.N.Pillai and M.V.Bhatt, J.Amer.Chem.Soc. 78, 3769 (1956); b. D.K.Banerjee and S.K.Balasubramanian, J.Org.Chem. 23, 105 (1958).

[2] *cf.* G.Stork, H.J.E.Loewenthal and P.C.Mukharji, J.Amer.Chem.Soc. 78, 501 (1956).

[3] a. L.Velluz, G.Nomine, J.Mathieu, E.Toromanoff, D.Bertin, J.Tessier and A.Pierdet, Compt.rend. 250, 1084 (1960); b. L.Velluz, G.Nomine, J.Mathieu, E.Toromanoff, D.Bertin, R.Bucourt and J.Tessier, Compt.rend. 250, 1293 (1960); c. L.Velluz, G.Nomine, J.Mathieu, E.Toromanoff, D.Bertin, M.Vignau and J.Tessier, Compt.rend. 250, 1510 (1960).



Demethylation of (Ib) with methyl magnesium iodide[4] at 175° gave the hydroxy phenol (IIa), m.p. 199-200°, in 79% yield. Partial acetylation of the hydroxy phenol (IIa) by refluxing with acetic acid and a catalytic amount of p-toluenesulphonic acid[5] gave the acetoxy phenol (IIb), m.p. 147°, in 42% yield. Hydrogenation of IIb in alcohol in the presence of 5% ruthenium--on-carbon catalyst[6] under 300 atm. pressure and at 100-110° gave a mixture

---

[4] a. A.L.Wilds and W.B.McCormack, J.Amer.Chem.Soc. 70, 4127 (1948); b. W.S.Johnson, E.R.Rogier and J.Ackermann, J.Amer.Chem.Soc. 78, 6322 (1956).

[5] C.Chen, Private communication; cf. Tetrahedron 3, 43 (1958).

[6] We are indebted to Baker & Co. for a gift of this catalyst.

which on chromatography over alumina yielded the hydroxy acetate (III) as the major product, m.p. 87-88°; 95°, besides small quantities of the hydrogenolysed material (VII), m.p.75°, and a gum. Oxidation of III by chromic acid in sulphuric acid and acetone[7] furnished the acetoxy ketone (IV), m.p. 144-145°; 152-153°. The gum on oxidation by the same method[7] gave mainly the above acetoxy ketone (IV) and a small amount of a stereoisomeric ketone (VI). The major product of the hydrogenation - oxidation sequence is assigned the configuration (IV) on the basis of Linstead's hypothesis of catalyst hindrance.[8] The axially oriented β-methyl group in IIb is likely to hinder the β-approach of the catalyst. The configuration (VI) of the isomeric oxidation product is based on analogy with the work of Robinson[9] and of Chen.[10] The addition of vinyl methyl ketone to the acetoxy ketone (IV) in presence of "Triton-B" under nitrogen proceeded in a completely stereospecific fashion to give the tetracyclic ketone (V), m.p. 172.5-173.5°. The alkylation is very likely to take place from the convex side (α) of the cis-decalin system (IV). All our stereochemical deductions were confirmed by establishing the identity of our synthetic

---

[7] C.Djerassi, E.R.Engle and A.Bowers, J.Org.Chem. 21, 1547 (1956).

[8] R.P.Linstead, W.E.Doering, S.B.Davis, P.Levine and R.R.Whetstone, J.Amer.Chem.Soc. 64, 1985 (1942).

[9] a. J.W.Cornforth, O.Kauder, J.E.Pike and R.Robinson, J.Chem.Soc. 3348 (1955); b. W.B.Renfrow and J.W.Cornforth, J.Amer.Chem.Soc. 75, 1347 (1953).

[10] C.Chen, see reference 5; Dr.Chen kindly informed us that the oestrane isomer to which he had earlier assigned the 5α,10β configuration was actually 5β,10β.

material with 8-isotestosterone obtained by Djerassi[11] from diosgenin by a comparison of their I.R. spectra.[12]

Works are in progress on the conversion of 8-isotestosterone to testosterone via 6,7-dehydro-8-isotestosterone and also on the preparation of 9-iso, 10-iso- testosterone from the isomeric acetoxy ketone (VI).

All compounds reported in this communication gave correct elementary analyses and infra-red and ultra-violet spectra.

---

[11] C.Djerassi, A.J.Manson and H.Bendas, Tetrahedron 1, 22 (1957).

[12] We are greatly indebted to Prof.C.Djerassi for a copy of the I.R. spectrum of the authentic 8-isotestosterone.

Tetrahedron Letters No. 12, pp. 27-32, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

A BIOGENETICALLY PATTERNED CONCEPT FOR THE LABORATORY SYNTHESIS OF CYCLIC COMPOUNDS

William S. Johnson and Russell A. Bell

Department of Chemistry, University of Wisconsin,

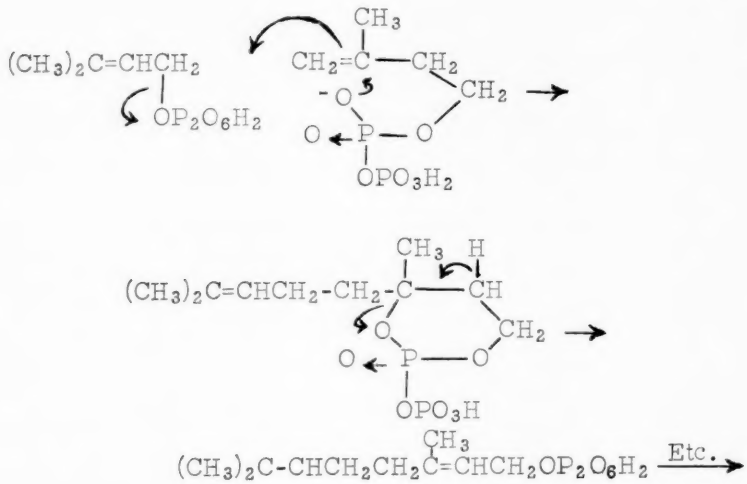
Madison, Wisconsin

(Received 15 April 1960)

THE key step in the polymerization of isopentenyl pyrophosphate, namely the C-C bond-forming stage, has been depicted[1] as a process involving alkylation of an isolated olefinic bond with an allylic cation-forming species (3,3-dimethylallyl pyrophosphate) under non-acidic ("physiological") conditions. There appears to be no in vitro precedent for the occurrence of such a reaction under neutral conditions. In biological systems the matter of unprecedented behavior can be dismissed by attributing special catalytic properties to the enzyme surface. But it is surely more attractive to hope to find some new chemical behavior, and in this case we chose to consider the hypothesis that the alkylation step is anchimerically assisted by participation of the pyrophosphate residue as indicated in the accompanying flow sheet. The tertiary alkyl phosphate linkage of the cyclized form would

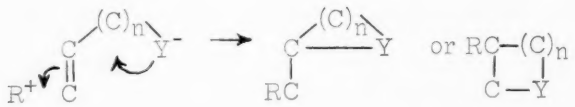
---

[1] F. Lynen, H. Eggerer, U. Henning and I. Kessel, Angew. Chem. 70, 739 (1958); H.C. Rilling and K. Bloch, J. Biol. Chem. 234, 1424 (1959); J.W. Cornforth, Tetrahedron Letters No. 19, 29 (1959).



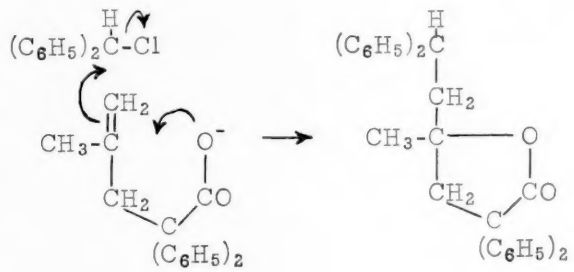
be expected to be unstable and collapse as indicated.

In considering models to test this hypothesis, we discovered that we were dealing with an apparantly unprecedented general reaction of the following type where Y^- is a nucleophilic function such as phosphate, amino, O of carbonyl, alkoxide O^-, carboxylate O^-, S^-, $^-CH(COOEt)_2$, etc.; and R^+ is a cationic species which might be derived from an alkyl halide, acid chloride, epoxide, C of carbonyl, etc., including vinylogous systems such as α,β-unsaturated ketones:



To test the premise, as well as to set up a model for the biochemical hypothesis, we chose to examine a case where $Y^- = COO^-$. When sodium 4-methyl-4-pentenoate was treated with simple alkyl halides it was not surprising to

find that only the ester was produced. In order to sterically inhibit alkylation of the carboxylate ion we turned to an extreme case, namely the reaction of sodium 2,2-diphenyl-4-methyl-4-pentenoate (I) with benzhydryl chloride. When a solution of these reactants in dimethyl formamide was allowed to stand at room temperature for four days, a γ-lactone, m.p. 128-129°,



I II

λ_{max} 5.72 μ, was isolated in over 60% (crude) yield. This substance was different from the known lactone,[2] m.p. 106-107°, λ_{max} 5.72 μ of the starting acid. That it was indeed the lactone of 2,2,6,6-tetraphenyl-4-methyl-4-hydroxy-hexanoic acid (II) followed from the analysis (Calc. for $C_{31}H_{28}O_2$: C, 86.08; H, 6.53. Found: C, 86.15; H, 6.62), the extinction coefficient of 890 at 261 mμ showing the presence of four phenyl groups, and the unique nmr spectrum, at 60 mc/sec which showed (CS_2 solution) a sharp singlet at -60.4 cps (relative to tetramethyl silane) corresponding to the 3 protons of the methyl group sttached to C_4; a doublet at -137.2 and -144 cps corresponding to two equivalent protons (at C_5) split (J = 6.8) by a single adjacent proton (at C_6); signals at -156.3 and -158.6 cps corresponding to two non-equivalent protons at C_3 and a well defined triplet at -232.4, -239.2 and

[2] P.N. Craig and I.H. Witt, J. Amer. Chem. Soc. 72, 4925 (1950).

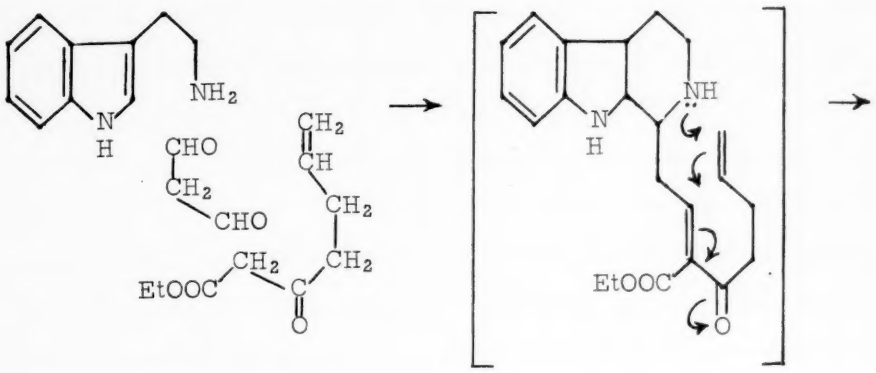
-246.0 cps, corresponding to a single proton (at C_6) split (J = 6.8) by two adjacent protons (at C_5). In addition to the aromatic proton absorption, a very weak band was found at -169.5 cps which corresponds to part of a quartet arising from spin-spin coupling (J = 12 cps) of the nonequivalent protons at C_3. The fourth (weak band) of the quartet, which would absorb at -145.5 cps is masked by the strong signal due to the C_5 protons.

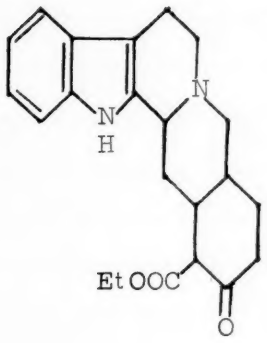
The production of the lactone II as described above bears a formal resemblance to the reaction of halogen with the sodium salt of a γ,δ-unsaturated acid to produce a δ-halo-γ-lactone, e.g. the reaction of bromine with I to produce the bromo lactone II (Br in place of benzhydryl).[2] The reaction with benzhydryl chloride, however, is basically different in that production of a new C-C bond is involved. Even if this type of reaction may have been carried out before, the general principle for thus producing new C-C bonds has not, to our knowledge, hitherto been recognized.

The scope of the concept is yet to be determined. An obvious limitation is the competing reaction involving interaction of R^+ directly with Y^- (ester formation in the example above), which can easily constitute the major course of the reaction. This difficulty promises to be obviated by a modification of the general scheme depicted above to include systems where R^+, as well as Y^-, is incorporated in the same molecule in such a way that their interaction is precluded, but so that they are juxtaposed, relative to the olefinic bond, for ring formation, viz.

$$^{+}R(C)_mC{=}C(C)_nY^{-} \longrightarrow \overbrace{R(C)_mC\text{-}C(C)_nY} \text{ or } \overbrace{R(C)_mC\text{-}C(C)_nY}$$

The following hypothetical scheme illustrates this modification and suggests its potential versatility:





It should be emphasised that this example is meant to serve only as a schematic illustration of the principle rather than as a proposed synthesis. The acid-catalyzed cyclization of certain polyenes[3] can be considered as a special case in this class, where the carbonium ion center is produced by

---

[3] G. Stork and A.W. Burgstahler, J. Amer. Chem. Soc. 77, 5068 (1955); P.A. Stadler, A. Eschenmoser, H. Schinz and G. Stork, Helv. Chim. Acta 40, 2191 (1957).

protonation of one olefinic bond, and another serves as the nucleophilic center. Our present study suggests that appropriate selection of functional groups may permit realization of cyclizations under neutral or even basic conditions to produce a wide variety of structures.

Another variation in the general concept, is the case where R^+, instead of Y^-, is incorporated in the olefinic portion of the molecule. Acid-catalyzed cyclizations of certain olefinic compounds may be considered as belonging to this class, e.g. the cyclization of butenyl-methylcyclohexene with sulfuric-acetic acid and acetic anhydride to give 9-methyldecalyl acetate,[4] but important variations under neutral conditions may now be anticipated.

It still remains to be shown whether the reaction of I with benzhydryl chloride is truly anchimerically assisted by the carboxylate group, or whether this anion serves to capture the carbonium ion formed by a rate-controlling attack of the benzhydryl cation on the olefinic bond, in which case the cyclization process still appears to play an important role in deciding the fate of the carbonium ion in a clean and selective manner. In any case our findings suggest the intermediacy of a cyclic form in the polymerization of isopentenyl pyrophosphate, and further studies of the general cyclization concept are indicated.[5]

---

[4] V.C.E. Brunop and R.P. Linstead, J. Chem. Soc. 720 (1940).

[5] Acknowledgment is made to the Wisconsin Alumni Research Foundation, the U.S. Public Health Service, and the National Science Foundation for support of this project.

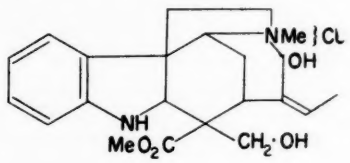
Tetrahedron Letters, No.12, pp. 33, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

ERRATA

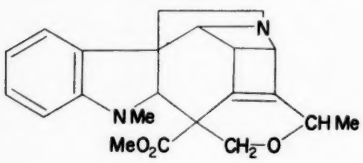
D. Chakravarti, R. N. Chakravarti, R. Ghose and Sir Robert Robinson, "Echitamine", Tetrahedron Letters No. 10, pp. 10-18 (1960).

p.11. Formula I should be:

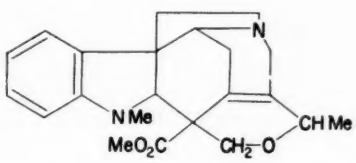


I

p.12. Formula V - delete a bond and for

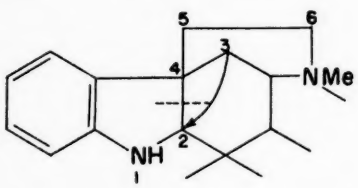


read

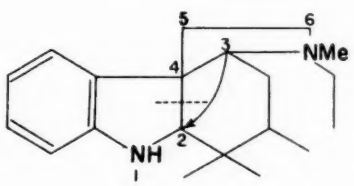


V V

p.17. Part of I - for



read



Part of I Part of I

19

Tetrahedron Letters No. 13, 1-8, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

THE ROLE OF IRON IN CARBONIUM ION REACTIONS OF FERROCENE DERIVATIVES

D. S. Trifan and R. Bacskai

Plastics Laboratory, Princeton University

Princeton, N. J.

(Received 6 May 1960)

Recently, some useful quantitative rate comparisons between certain metallocenyl and triphenyl systems were provided by Richards and Hill[1] for solvolysis reactions proceeding via α-metallocenyl carbonium ions which showed the solvolysis rates in 80% acetone-water mixture at 30° for metallocenyl carbinyl acetates to be on the same high order of magnitude as triphenylcarbinyl acetate. Included in their series was the heteroannular acetate, α-acetoxy-1,1'-trimethyleneferrocene which was observed by these authors to proceed more slowly than the analogous open chain compound,

---

[1] J. H. Richards and E. A. Hill, J. Amer. Chem. Soc., 81, 3484 (1959).

[2] Calculated from data of Richards and Hill[1], although the value 132 is used in their text.

methylferrocenylcarbinyl acetate, by a factor of 29 [2], a rate depression which they attributed to the structurally enforced non-planarity of the resulting carbonium ion. But to account for the fact that this heteroannular compound nevertheless still underwent solvolysis via a carbonium ion mechanism, they suggested for this special case the possibility that stabilization of the non-planar ion might be obtained by participation of the iron electrons.

Work on a comprehensive series of ferrocenyl alcohols has been in progress in this laboratory for an extended period of time, studying and defining the active and general role of the iron atom and its electrons acting as proton acceptors in intramolecular hydrogen bonding reactions[3]. Especially since the suggestion of Richards and Hill had been limitedly made only to account for the special case of the enforced non-planar ion, and the overall high solvolytic reactivities were considered to be in consistent accord with M.O. treatment for metallocenyl systems[4], it was therefore of interest to us to apply experimental tests to ascertain that metal electron participation might here too be a completely general

---

[3] D. S. Trifan and R. Bacskai, unpublished results.

[4] J. H. Richards, Abstracts 135th Meeting of American Chemical Society, April 5-10, 1959, Boston, Mass., p. 86-O.

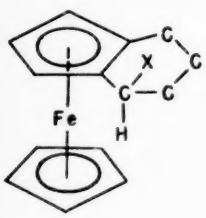
1960

phenomenon for the chemical reactions of all suitably constituted metallocene compounds proceeding via α-cationic intermediates.

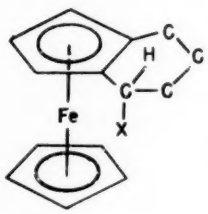
In this preliminary report we wish to present briefly some results on the role of the metal atom with respect to rates and stereochemistry which appear to be of fundamental importance and generality for all metallocene reactions of this type.

General Metal Participation

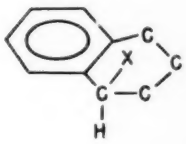
Two ferrocene derivatives of great utility in studying the role of the iron atom in this and related respects are the two isomeric α-substituted 1,2-tetramethyleneferrocenes, represented by structures I and II and designated exo- and endo-, respectively.



I



II



III

From the corresponding ketone[5], the isomeric alcohols, I and II (X = OH), were prepared by $LiAlH_4$ reduction. Separation of the two alcohols (11% exo-, m.p. 71.5-72.5°; 89% endo-, oil) and ready assignment of the correct corresponding structure by at least four unequivocal and independent criteria provided the necessary materials for the preparation of the exo- and endo-acetates, I and II (X = $OCOCH_3$), m.p. 64-65° and 49-50°, respectively, for comparative solvolysis rate measurements. The analogous phenyl ester, α-tetralyl acetate, III (X = $OCOCH_3$), b.p. 156°/25 mm., was also included for comparative rate purposes.

The data summarized in Table 1 show a large rate gap between the exo- and endo-isomers resulting from the difference in relative geometry between the iron atom and the departing substituent and permit the important conclusion that in the exo- case (I) where the iron atom is located backside to the acetoxy group, the iron electrons are participating in a backside displacement of the anion in the rate determining ionization process. Where backside geometry between the iron and acetoxy group cannot be attained, as in

---

[5]K. L. Rinehart, Jr. and R. J. Curby, Jr., J. Amer. Chem. Soc., 79, 3290 (1957).

1960

TABLE 1. Solvolysis rates[a] in 80% acetone-water at 30°.

COMPOUND	k, sec^{-1}	Rel. rate
<u>exo</u>-α-Acetoxy-1,2-tetramethylene-ferrocene (I, X = $OCOCH_3$)	7.43×10^{-4}	2240
<u>endo</u>-α-Acetoxy-1,2-tetramethylene-ferrocene (II, X = $OCOCH_3$)	3.31×10^{-7} [b]	1
α-Tetralyl acetate (III, X = $OCOCH_3$)	5.50×10^{-10} [b]	0.00166
Methylferrocenylcarbinyl acetate (IV)	1.84×10^{-4}	556

[a] Clean first order kinetics were observed in all cases. Reactions were followed to 80-90% for the ferrocene derivatives.

[b] Extrapolated from data at higher temperatures.

the constrained <u>endo</u>- structure (II), no such iron participation is possible and a sharp 2240-fold drop in rate is observed. This rate factor is significant in terms of evidence of iron electron participation in the rate step since it is entirely reflected in the enthalpy of activation, $\Delta H^{\ddagger}$. Also, since side chains are usually not rotationally constrained as in the test structures I and II, and suitable backside geometry between the iron atom and substituent group is readily attainable, it is clear from the comparable high order of

solvolysis rates for such ferrocene derivatives in general, e.g. ferrocenylmethylcarbinyl (IV), etc.[1], that iron electron participation must be occurring as a characteristic and general phenomenon in reactions proceeding through α-ferrocenyl cationic intermediates. Analogously, the same metal electron participation must be occurring for reactions involving other metallocenyl cations, judging from the even greater solvolysis rates of the osmocenyl and ruthenocenyl examples[1].

The rate contrast between the endo-isomer, II (X = $OCOCH_3$) and α-tetralyl acetate, III (X = $OCOCH_3$), would appear at first to suggest that some residual electronic driving force is still present in the endo-isomer compared to its phenyl analog. However, this is not the case as shown by the fact that the $\Delta H^{\ddagger}$ of activation of the two compounds are actually in the reverse sequence. The rate difference here is due instead to a much smaller negative entropy of activation, $\Delta S^{\ddagger}$, for the ferrocenyl compared to the phenyl compound, an observation which applies generally for all of the ferrocenyl-phenyl parrs we have measured to date.

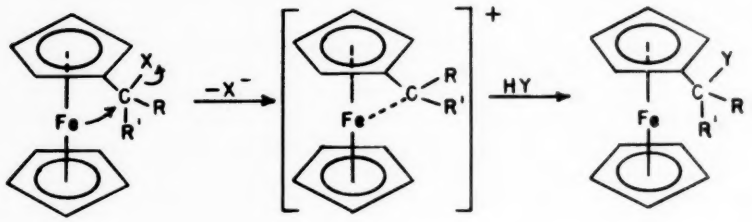
Cation Structure and Stereochemistry

A second important finding which has resulted from this study concerns the structure and stereochemistry of

1960

α-ferrocenyl carbonium ions.

Evidence for the metallocarbocation structure, VI,



V VI VII

involving covalent bonding between the iron atom and the carbonium carbon comes from the absolute stereochemical purity of the exo-alcohol I (X = OH) which is the sole alcohol product found in the 80% acetone-water solvolyses of both exo- and endo-esters. With the precision available from our chromatographic and infrared spectroscopic methods, it was possible to establish that I ($X = OCOCH_3$) and II ($X = OSO_2C_6H_4CH_3$) both proceeded to I (X = OH) with a purity of not less than 99.6 and 99.94%, respectively. This highly stereospecific result may be compared with the 89:11 endo-: exo-alcohol ratio from the $LiAlH_4$ reduction of the ketone which provides an approximate (but reversed) indication of the ratio of exo-: endo-solvent attack which might have been

expected if final solvolysis product had been produced via a non-bonded classical-type ion.

While the anchimerically unassisted solvolysis of II must first have proceeded through a planar classical-type ion which quickly transformed into the stabler metallocarbonium ion structure (VI) before any reaction with solvent could proceed, solvolysis of I where metal electron participation occurs can lead directly to the metallocarbonium ion. Thus, in the general case of open-chain derivitives, V $\longrightarrow$ VI $\longrightarrow$ VII, one would therefore expect reaction to proceed with overall retention of configuration as a consequence of metal electron participation and cation structure.

A final pertinent topic of interest here is the question of possible iron participation and cation structure for β-metallocenyl derivatives. Results to date show a solvolysis rate factor in 80% acetone-water of 537 for β-ferrocenylethyl vs. β-phenylethyl p-toluenesulfonates, of which only a factor of *ca.* 3 is reflected in the $\Delta H^{\ddagger}$ terms, however.

The extent to which iron participation may still be influencing rate and stereochemistry remains under study through appropriate rate and stereochemical experiments. These results and a fuller presentation of the above data will be published subsequently.

Tetrahedron Letters No.13, pp. 9-13, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

SOLVENT EFFECTS ON THE ISOMER DISTRIBUTION IN THE CHLORINATION OF AROMATICS

Leon M. Stock and Albert Himoe

Department of Chemistry, University of Chicago, Chicago 37, Illinois

(Received 9 May 1960)

A recent kinetic investigation of the non-catalytic chlorination of benzene and certain methylbenzenes in acetic acid, nitromethane, acetonitrile and ethylene dichloride demonstrated significant variations in the rates and relative rates of nuclear substitution.[1] An examination of the rate data for the chlorination in acetonitrile by the treatment devised by Condon[2] indicated a significant change in the isomer ratio for toluene from that obtained for the reaction in acetic acid.[3] This conclusion prompted an investigation of the products of the chlorination of toluene in several solvents.

The observations for this reaction are summarized in Table I.

As demonstrated in Table I, the isomer ratio has been found to depend on the solvent. The hydroxylic solvents have been observed to yield approximately 60% o- and 40% p-chlorotoluene. On the other hand, non-hydroxylic solvents provided an inverse product ratio. Intermediate isomer distributions were obtained in the mixed solvents investigated. For example, in acetonitrile, 5.5 M water, the products were analyzed as 51% o- and 49% p- isomer;

---

[1] L. J. Andrews and R. M. Keefer, J. Am. Chem. Soc., 81, 1063 (1959).

[2] F. E. Condon, ibid., 70, 1963 (1948).

[3] H. C. Brown and L. M. Stock, ibid., 79, 5175 (1957).

Table I

Isomer Distributions for the Non-Catalytic Chlorination of Toluene at 25°

Solvent	Chlorotoluene,[a] % o-	p-
Acetic acid[b]	60	40
Acetic acid, 15.3 M H_2O[c]	61	39
Pivalic acid	64	36
Trifluoroacetic acid	67	33
Water, 5 M HCl[d]	69	31
t-Butyl alcohol	59	41
Nitromethane	34	66
2-Nitropropane	47	53
Acetonitrile	38	62
Ethylene dichloride	41	59

[a]Analyses (± 2% of reported value) by vapor phase chromatography.

[b]Ref. 3. [c]Four other aqueous solvents have been examined with essentially identical results, ref. 6.

[d]Heterogeneous.

while in acetonitrile, 11.1 M water, the isomer distribution was 54% o- and 46% p-product.

The greater selectivity of the chlorinating agent in nitroparaffins suggested the utilization of this solvent to achieve predominant p-substitution. This expectation has been confirmed for the chlorination of t-butylbenzene and anisole as representative aromatic substrates. Thus, the chlorination of t-butylbenzene in 2-nitropropane yielded 95% p-chloro-t-butylbenzene

in contrast to only 76% p-isomer for the reaction in acetic acid.[4] The chlorination of anisole in 2-nitropropane gave less than 1% of the o-isomer compared with 24% of this product from the reaction in acetic acid.[5] Clearly, the solvent provides a convenient variable for effecting the preparation of many p-substituted halobenzenes essentially free of contamination with the o-isomer.

1960

Several factors have been examined in an attempt to account for the variation in the isomer distributions. Certain quantitative kinetic observations are summarized in Table II.

Table II

Rates, Relative Rates and Partial Rate Factors for the Chlorination of Benzene and Toluene at 25°

Solvent	$10^3 k_2$ l·mole^{-1} sec.$^{-1}$ for Benzene	Relative Rate for Benzene	Partial Rate Factors $k_{o\text{-}Me}/k_H$	$k_{p\text{-}Me}/k_H$
Acetic acid[a]	0.0015	1.0	617	820
Aqueous acetic acid[b]	4.5	3.0×10^3	605	701
Trifluoroacetic acid[c]	7	4.6×10^3		
Nitromethane[c,d]	0.006	4.0	2000	8000
Acetonitrile[c,d]	.0009	0.6	1700	5600

[a]Data from ref. 3. [b]Solvent composition: 20.8 M H_2O, 1.2 M HCl; data from ref. 6.

[c]Kinetic observations from ref. 1. [d]Partial rate factors based on experimental isomer distributions, Table I.

[4]L. M. Stock and H. C. Brown, ibid., 81, 5615 (1959).

[5]B. Jones and E. N. Richardson, J. Chem. Soc., 3939 (1955).

From the observations presented in Tables I and II, it is apparent that the product ratios cannot be attributed to changes in the absolute rate of reaction. Indeed, in acetic acid and aqueous acetic acid solvent, the rate of chlorination changes by a factor of 3000 while the product distribution remains unchanged.[6] The experimental results also fail correlation on the basis of the dielectric constant of the reaction media as has been suggested to account for the variable isomer distributions observed in the nitration of phenol.[7]

A significant observation is the unchanged selectivity for the chlorination of toluene in dry and aqueous acetic acid, i.e. under conditions leading to a large change in the rate of reaction.[6] This result suggests the presence of a common intermediate electrophilic chlorination reagent.[8] The negligible influence of acids and bases on the rate of reaction in dry and aqueous acetic acid[6] and the selective properties of the reagent eliminate the highly reactive chloronium ion[11] from consideration. These data are compatible with molecular chlorine as the reagent. However, the chlorination of

---

[6] L. M. Stock, Abstracts 137th Meeting American Chemical Society, Cleveland, Ohio, April 1960, p. 52-O.

[7] J. Podkowka and A. Tarnawski, Monatsh., 90, 179 (1959).

[8] Variations in absolute rate with virtually unchanged partial rate factors for nitration[9] and acylation[10] have been attributed to common electrophilic intermediates.

[9] E. D. Hughes, C. K. Ingold and R. J. Reed, ibid., 2400 (1950).

[10] F. R. Jensen and H. C. Brown, J. Am. Chem. Soc., 80, 3039 (1958).

[11] P. B. D. de la Mare, J. T. Harvey, M. Hassan and S. Varma, J. Chem. Soc., 2756 (1958).

1960

toluene in other solvents leads to major variations in the relative rates and isomer distributions, Tables I and II. In view of these results, we are led to the suggestion that the effective reagent is a complex between molecular chlorine and the solvent.[12]

In addition to the variation in selectivity of the reagent, specific solvation of the components of the electron deficient transition state must be invoked to account for the large variations in rate. These two factors provide a rational explanation for the change in rate and selectivity in aromatic chlorination.

Moreover, the variation in the ortho to para ratio is accommodated by this interpretation. Selective chlorination reagents, e.g. in nitroparaffins, will be more sensitive to the steric requirements of substituent groups in the substrate. On the other hand, it is possible to attribute the variation in isomer distribution to the increased steric requirements of the complexed chlorine molecule. These suggestions and the general problem of solvent effects on aromatic halogenation are currently under investigation in this laboratory.

The authors are grateful to the Research Corporation for support of this work.

---

[12] A similar explanation has provided a reasonable interpretation for the influence of solvent on free radical chlorination. G. A. Russell, J. Am. Chem. Soc., 80, 4987, 4997, 5002 (1958).

Tetrahedron Letters No.13, pp. 14-18, 1960. Pergamon Press Ltd. Printed in Great Britain.

EFFECT OF SOLVENTS UPON THE INITIAL OZONE ATTACK ON POLYCYCLIC AROMATICS

Frank Dobinson and Philip S. Bailey

Department of Chemistry, University of Texas, Austin, Texas

(Received 2 May 1960)

Recent studies[1-9] concerning the ozonation of polycyclic aromatic compounds have indicated that the major ozone attack occurs with some systems at the positions of lowest ortho (or bond) localization energy[10] and with other systems at the positions of lowest para localization energy[10]. These findings have been explained in two analogous ways: (1) the preferred ozone attack occurs via a rate-controlling transition state whose geometry corresponds to the most stable dihydro compound (i.e. 1,2 or 1,4) as measured by the appropriate corrected quinone -- hydroquinone redox potentials[5,8]; (2) the preferred ozone attack occurs at the ortho or para

---

1 P. S. Bailey, Chem. Rev. 58, 965 (1958).
2 P. G. Copeland, R. E. Dean and D. McNeil, Chem. & Ind. 329 (1959).
3 P. G. Copeland, R. E. Dean and D. McNeil, Chem. & Ind. 98 (1960).
4 F. T. Wallenberger, Tetrahedron Letters No. 9, p.5, 1959.
5 E. J. Moriconi, W. F. O'Connor and F. T. Wallenberger, J. Amer. Chem. Soc. 81, 6466 (1959).
6 E. J. Moriconi, W. F. O'Connor and L. B. Taranko, Arch. Biochem. Biophys. 83, 283 (1959).
7 E. J. Moriconi, G. W. Cogswell, W. J. Schmitt and W. F. O'Connor, Chem. & Ind. 1591 (1958).
8 E. J. Moriconi, W. F. O'Connor, L. B. Taranko, B. Rakoczy and B. P. Fürer, paper presented at the 136th national meeting of the American Chemical Society, Atlantic City, N. J., September, 1959.
9 P. S. Bailey and J. B. Ashton, J. Org. Chem. 22, 98 (1957).
10 M. J. S. Dewar, J. Amer. Chem. Soc., 74, 3357 (1952).

positions corresponding to the lowest calculated resonance energy decrease accompanying the formation of the transition state[4].

Although these suggestions were able to correlate the data at hand at the time, they do not consider the possibility that the type of ozone attack, transition state and intermediate produced may vary with the type of solvent employed during the ozonation. The yields of ozonation products from some of the polycyclic aromatics were significantly low[2,3,5-8] and in some cases no information was given concerning the solvents employed[2,3].

Results of ozonation studies with anthracene suggest, but do not prove, the existence of a solvent effect. Ozonation of anthracene in acetic acid resulted in yields up to 69% of anthraquinone[9], whereas ozonation in carbon tetrachloride led to 62-67% yields of phthalic acid and only 6-14% yields of anthraquinone[11].

Using 9,10-dibromoanthracene as our aromatic species we have now obtained proof that there are two competing types of initial ozone attack and that the one which predominates can be determined by the type of solvent employed. Ozonation of this substance in methanol-methylene chloride medium followed by an oxidative work-up using hydrogen peroxide resulted in 79-80% yields of anthraquinone (m.p. 284-286°). Two mole-equivalents of ozone were absorbed during the reaction and some molecular bromine was released. Hydrogen peroxide was shown not to attack the starting material under the reaction conditions employed. Ozonolysis in methylene chloride followed by an oxidative work-up procedure gave only 18-22% yields of

---

[11] P. S. Bailey, J. B. Ashton and F. Dobinson, unpublished results.

anthraquinone and 75-82% yields of 3,6-dibromobenzene-1,2,4,5-tetracarboxylic acid (m.p. above 300°). Found: C, 29.34; H, 1.20; Br, 38.94. $C_{10}H_4Br_2O_8$ requires: C, 29.15; H, 0.98; Br, 38.80%. This acid was made previously by the nitric acid oxidation of 1,4-dibromo-2,5-diethyl-3,6-dimethylbenzene[12]. We established its identity by catalytic dehalogenation to pyromellitic acid (m.p. 270-271°) which showed no depression in a mixture melting point with an authentic sample. Thus the position of major ozone attack has been changed from one aromatic ring to another simply by changing the type of solvent used. This could happen only if a drastic change in the mechanism of the ozone attack accompanied the solvent change.

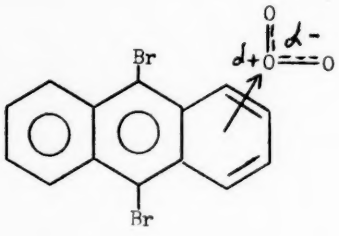
The major attack in methylene chloride appears to involve essentially a four-center ozone attack leading to a transition state similar to that described by Moriconi, Wallenberger and coworkers[4,5,8] and producing a five-membered ring intermediate (II). Probably a π complex of type I is a precursor to the transition state leading to II. After the attack at the 1,2-bond the reaction continues at the 3,4 and 5,6 and 7,8 bonds. The presence of bromo groups at the 9 and 10 positions inhibits a four-center attack on the middle ring.

A reasonable explanation for the results in the presence of methanol is that the ozone molecule is polarized by the solvent (e.g. III) and makes an ionic attack at the reactive 9 position. This would involve a different transition state, leading to the formation of an intermediate sigma complex (IV). The route from IV to products is uncertain. Either

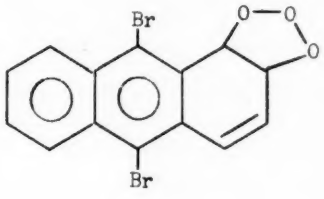
---

[12] E. Philippi, Liebigs Ann. 428 286 (1922).

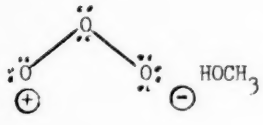
1960



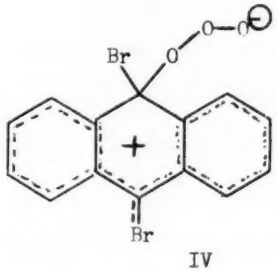
I



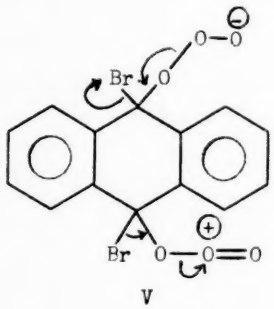
II



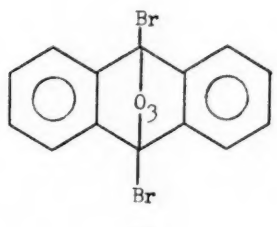
III



IV



V



VI

a second ozone molecule could attack nucleophilically[13] to give V which

---

13 A. H. Riebel, R. E. Erickson, C. J. Abshire and P. S. Bailey, J. Amer. Chem. Soc. 82, 1801 (1960).

could go to products as shown, or else a 1,4-addition could be completed to give VI which could decompose to products through the reducing action of methanol.

The competition between an ionic and a four-center attack of ozone seems to be quite general. The yield of product from an ozone attack in a 1,2 sense with dibenz [a,h] anthracene was considerably lower in the presence of methanol than with pure methylene chloride solvent[8]. We shall report later further evidence for this competition with anthracene, pyrene and certain furans.

The observation of the type of solvent effect described here is novel in ozonation reactions. We feel that it is important not only because of its mechanistic implication but also because of its potential utility in organic syntheses.

The authors gratefully acknowledge support of this work by grants from the Robert A. Welch Foundation and the National Science Foundation.

Tetrahedron Letters No.13, pp. 19-22, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

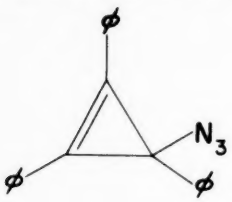
THE REARRANGEMENT OF 1-AZIDO-1,2,3-TRIPHENYLCYCLO-PROPENE TO 4,5,6-TRIPHENYL-v-TRIAZINE

E. A. Chandross and G. Smolinsky

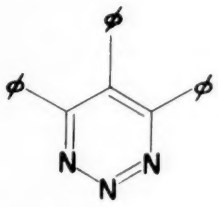
Bell Telephone Laboratories, Inc., Murray Hill, New Jersey

(Received 13 May 1960)

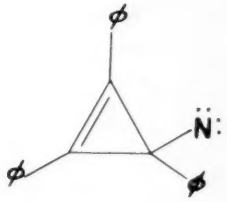
WE wish to report the preparation of 1-azido-1,2,3-triphenylcyclopropene (I) and its facile rearrangements to 4,5,6-triphenyl-v-triazine (II), a derivative of a hitherto unknown ring system.[1] This work was originally undertaken in order to attempt the conversion of I to the corresponding hypothetical nitrene (III),[2] an intermediate which appeared capable of undergoing several interesting rearrangements.



I



II



III

The addition of excess sodium azide to a solution of 1,2,3-triphenylcyclo-

---

[1] J. G. Erickson in The Chemistry of Heterocyclic Compounds, Vol. X, Chap. I. Interscience, New York (1956).

[2] G. Smolinsky, J. Amer. Chem. Soc. In press, and references therein.

propenyl bromide[3] in dimethylformamide followed by an aqueous workup gave a liquid which is assigned the structure of the azide I on the basis of the following evidence: (i) its I.R. spectrum contained a strong band at 4.75μ, characteristic of aliphatic azides,[5] (ii) its U.V. spectrum was essentially identical to that of 1-methoxy-1,2,3-triphenylcyclopropene (IV),[6] (iii) it was converted to IV on treatment with sodium methoxide in methanol. The azide I decomposed at a moderate rate at room temperature and rapidly in boiling xylene with the formation of two products. One of these, isolated in 45% yield, was a colorless, crystalline solid II (m.p. 276° dec.) isomeric with I (Found: C, 81.49; H, 4.98; N, 13.24; M.W. 306. Calc. for $C_{21}H_{15}N_3$: C, 81.53; H, 4.89; N, 13.58; M.W. 309.) The I.R. spectrum (KBr) of II had no band below 6μ other than aryl C-H; the U.V. spectrum showed λ_{max}^{EtOH} 262 mμ (21,400), 278 mμ (shoulder, 15,500) and 297 mμ (shoulder, 8,100) and was unchanged in the presence of dilute HCl. II was converted to 3,4,5,-triphenylpyrazole (V)[7,8] upon reduction in acetic acid solution with either zinc or hydrogen over palladium and was readily hydrolyzed to 1,2,3-triphenylpropane-1,3-dione (VI)[7] by the action of hydrochloric acid in hot acetic acid.

---

[3] This salt was prepared by the reaction of benzal chloride, potassium t-butylate and diphenylactylene in benzene followed by reaction of the resulting, unisolated 1-t-butoxy-1,2,3-triphenylcyclopropene with anhydrous hydrogen bromide, a method which, unknown to us, had previously been developed by Breslow.[4]

[4] R. Breslow. Private communication.

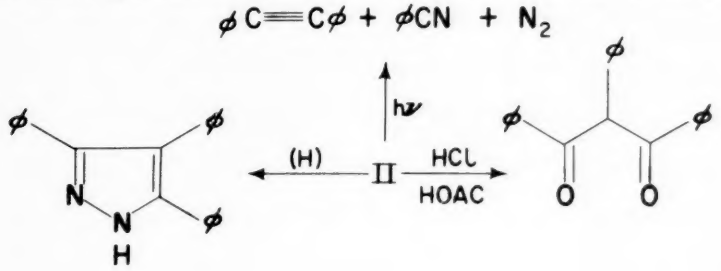
[5] E. Lieber, C.N.R. Rao, T.S. Chao and C.W.W. Hoffman, Analyt. Chem. 29, 9161 (1957).

[6] R. Breslow and C. Yuan, J. Amer. Chem. Soc. 80, 5990 (1958).

[7] Identified by comparison with an authentic sample.

[8] Cf. The behavior of the related 1,2,4-triazines upon reduction, R. Metze, G. Rolle and G. Scherowsky, Chem. Ber. 92, 2481 (1959).

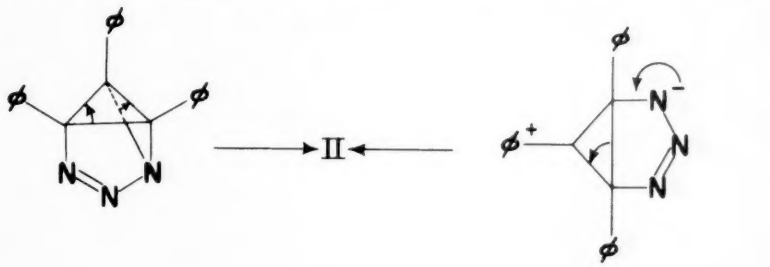
Furthermore, II is sensitive to light and was destroyed by irradiating a stirred suspension in benzene with a sunlamp for 12 hr. The crude product smelled strongly of benzonitrile and an examination of the I.R. spectrum suggested the presence of benzonitrile (4.45μ) and diphenylacetylene; the latter was isolated in 72% yield.[7] These transformations and the spectral and analytical data can be rationalized only on the basis of the structure 4,5,6-triphenyl-v-triazine (II). The ready hydrolysis and photolysis of



V VI

II are indicative of a loss in aromatic character of this ring system, probably a consequence of the presence of the v-triazine linkage.

The formation of II may be explained by the intramolecular addition of the azide group to the double bond[9] present in I, forming VII, followed by



VII VIII

[9] J.H. Boyer and F.C. Canter, Chem. Rev. 54, 1 (1954).

collapse of this highly strained species to II. Alternatively, one may postulate electrophilic attack on the cyclopropene double bond by the azide group with the formation of VIII, a valence tautomer of II. These paths are closely related and cannot be distinguished on the basis of the data now available.

A yellow solid, m.p. 235° dec., $C_{42}H_{30}N_2$ (Found: C, 90.07; H, 5.46; N, 4.90; M.W. 480) was also isolated (13%) from the pyrolysis of I in xylene. It had no band in the I.R. below 6μ other than aryl C-H and showed λ_{max}^{EtOH} 247 mμ (49,000), shifting to 263 mμ (25,000) in dilute HCl. It did not arise by the decomposition of II since the triazine was recovered unchanged when subjected to the pyrolysis conditions. This compound may arise via loss of N_2 from I accompanied by rearrangement and dimerization; the simple dimerization of the nitrene III is precluded as the resulting azo compound would be thermally labile and would probably decompose with loss of nitrogen. We have not as yet been able to establish the structure of this product and further work is in progress.

Note added in proof: Professor Breslow has informed us that he has isolated a product corresponding to II from the reaction of sodium azide with 1,2,3-triphenylcyclopropenyl bromide in boiling tetrahydrofuran.

Tetrahedron Letters No.13, pp.23-29, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

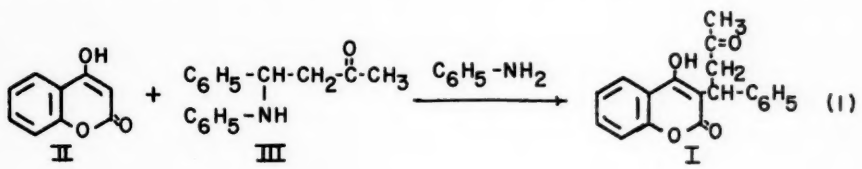
THE MECHANISM[1] OF WARFARIN[2] FORMATION FROM 4-HYDROXYCOUMARIN AND β-ANILINOBENZYLACETONE. EVIDENCE FOR SCHIFF BASE INTERMEDIATES SHOWING ENHANCED REACTIVITY IN THE MICHAEL REACTION

Collin Schroeder, Seymour Preis and Karl Paul Link

University of Wisconsin, Madison, Wisconsin

(Received 15 April 1960; in revised form 16 May 1960)

PREVIOUS kinetic studies[3] have shown that the formation of warfarin (I) from 4-hydroxycoumarin (II) and β-anilinobenzylacetone (III) in the presence of aniline (reaction 1) is more rapid (ca. double at equivalent concentrations)



II III I (1)

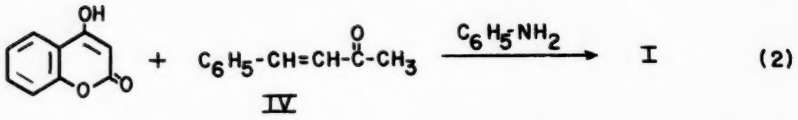
than its formation from 4-hydroxycoumarin and benzalacetone (IV) in the presence of aniline (reaction 2).

---

[1] In the Japanese Patent Court demandant Toko Chemical Co., Ltd., Tokyo, Japan, for H. Naruke "on the scope of right of patent number 195, 040 held by Wisconsin Alumni Research Foundation, Madison 5, Wisconsin, Trial No. 380/1953" dated October 26, 1953, it is asserted that the formation of warfarin from 4-hydroxycoumarin and β-anilinobenzylacetone is a direct (S_N2) reaction.

[2] The chemical name 3-(α-acetonylbenzyl)-4-hydroxycoumarin is the systematic name selected by Chemical Abstracts for the anticoagulant warfarin.

[3] C.H. Schroeder, Tien-Hui Lin, E.L. King and K.P. Link, Abstracts of Papers, the 136th Meeting of the American Chemical Society, Atlantic City, New Jersey, September 13-18, 1959, p. 109-p.



These results supported the conclusion that the usual mechanism of the Robinson modification[4a,b] of the Michael reaction is not operative. That is, (a) the elimination of aniline from β-anilinobenzylacetone to give benzalacetone and (b) the condensation of benzalacetone with 4-hydroxycoumarin to give warfarin, occurs only to a minor extent.

The first clue on the role of aniline in reaction 1 was obtained when it was found that tertiary amines (e.g. triethylamine, triethylenediamine,[5] pyridine) are poor catalysts for the formation of warfarin in this reaction. This similarity to the well-known Knoevenagel condensation in which tertiary amines are less effective as catalysts suggested like mechanisms.

Reactive Intermediates

It has been proposed[6 - 9a] on the basis of kinetic evidence that the active species in the Knoevenagel reaction is a condensation product of the

---

4a F.J. McQuillin and R. Robinson, J. Chem. Soc. 1097 (1938); b For a discussion of this method and a review of the Michael reaction see E. Bergmann, D. Ginsburg and R. Pappo in R. Adams, Organic Reactions Vol. 10, Chapter 3. John Wiley, New York (1959); c Ibid. pp. 207, 241.

5 DABCO-grade 1,4-diazo [2.2.2] bicyclooctane was obtained from Houdry Process Corp., Philadelphia, Pa.

6 E. Knoevenagel, Ber. Dtsch. Chem. Ges. 31, 2596 (1898).

7 F.H. Westheimer and H. Cohen, J. Amer. Chem. Soc. 60, 90 (1938).

8 T.I. Crowell and D.W. Peck, J. Amer. Chem. Soc. 75, 1075 (1953).

9a C.K. Ingold, Structure and Mechanism in Organic Chemistry p. 685 Cornell University Press, Ithaca, N.Y. (1953); b Ibid. p. 694.

primary or secondary amine with the carbonyl group. Therefore, in an effort to extend and test this proposal the anils of β-anilinobenzylacetone and of benzalacetone were prepared.

β-Anilinobenzylacetone anil (m.p. 135°, infrared spectrum: N-H, 2.95 μ; -C=N-, 6.02 μ. (Found: C, 83.5; H, 7.2. Calc. for $C_{22}H_{22}N_2$: C, 84.0; H, 7.0)) was obtained in low yield by heating a mixture of aniline and β-anilinobenzylacetone. This anil can be more readily obtained by the azeotropic distillation of water from a reaction mixture containing either benzalacetone or β-anilinobenzylacetone, aniline and an acid catalyst whose acidity (pK'a) in comparable systems is essentially in the range of acetic acid (i.e. 4-hydroxycoumarin, warfarin, dihydroresorcinol, barbituric acid, lawsone, ascorbic acid, certain ion exchange resins, etc.).

Benzalacetone anil (m.p. 108-110°, infrared spectrum -C=N- of an α,β-unsaturated system,[10] 6.15 μ. (Found: C, 86.9; H, 6.7. Calc. for $C_{16}H_{15}N$: C, 86.9; H, 6.8) was also obtained in low yield from these reaction mixtures.

The role of the two anils as intermediates in the formation of warfarin in reaction 1 is demonstrated by yield comparison studies. Benzalacetone, β-anilinobenzylacetone, β-anilinobenzylacetone anil and benzalacetone anil were each allowed to react with 4-hydroxycoumarin under similar conditions. The results are given in Table 1.

These results show that β-anilinobenzylacetone anil and benzalacetone anil react with 4-hydroxycoumarin to form warfarin much more rapidly than either β-anilinobenzylacetone or benzalacetone.

Although the degree of enhanced reactivity of the Schiff base system must await a thorough kinetic analysis, it can be said that the ethylenic

---

[10] H.R. Nace and E.P. Goldberg, J. Amer. Chem. Soc. 75, 3646 (1953).

Schiff base benzalacetone anil and the Schiff base β-anilinobenzylacetone anil show substantial increased reactivity. These Schiff base systems react at least 25 times faster than the β-anilinobenzylacetone-aniline system and at least 50 times faster than the benzalacetone-aniline system.

TABLE 1[a].

Formation of warfarin from 4-hydroxycoumarin[b] plus acceptors related to benzalacetone

Acceptor	Acceptor (moles/l.)	Aniline (moles/l.)	Warfarin (% yield)
$C_6H_5-CH=CH-\overset{O}{\overset{\|}{C}}-CH_3$	0.117	0.234	Less than 4[c]
$C_6H_5-\underset{C_6H_5-NH}{\underset{\|}{CH}}-CH_2-\overset{O}{\overset{\|}{C}}-CH_3$	0.117	0.117	Less than 4[d]
$C_6H_5-\underset{C_6H_5-NH}{\underset{\|}{CH}}-CH_2-\underset{N-C_6H_5}{\underset{\|}{C}}-CH_3$	0.117	none	76
$C_6H_5-CH=CH-\underset{N-C_6H_5}{\underset{\|\|}{C}}-CH_3$	0.117	0.117	72
$C_6H_5-CH=CH-\underset{N-C_6H_5}{\underset{\|\|}{C}}-CH_3$	0.117	none	71
$C_6H_5CH=CH-\overset{O}{\overset{\|}{C}}-CH_3$	0.175	0.350	17
$C_6H_5\underset{C_6H_5NH}{\underset{\|}{CH}}-CH_2-\overset{O}{\overset{\|}{C}}-CH_3$	0.175	0.175	25

[a] Each reaction took place in refluxing dioxane for 60 min. These conditions were the same as those used in the kinetic studies.[3]

[b] The initial concentration of 4-hydroxycoumarin (moles/l.) was equal to the initial concentration of the acceptor in each case.

[c] On the basis of the rate law[3] a 3% yield of warfarin can be calculated for these conditions.

[d] This yield was estimated to be one half that of part c or 1.5%.[3]

An overall mechanism consistent with the above results and the kinetics[3,11] is given. The acid HX in the scheme is provided by the Michael donor 4-hydroxycoumarin (pKa 4.1). A non-donor acid such as acetic acid can be used to catalyze this reaction.

The mechanism provides a reasonable rationalization for the function of the Knoevenagel type catalysts when they are used in the Michael reaction with α,β-unsaturated carbonyl acceptors (or their Mannich base precursors).[9b]

It is noteworthy that the reaction of benzalacetone anil with 4-hydroxycoumarin appears to be the first example of a Michael reaction initially involving the open-chain conjugated system of the type $-\overset{|}{C}=C-C=N-$.[4b,c] (See also Adams and Reifschneider).[12]

In Situ Formation of the $-\overset{|}{C}=C-C=N-$ System

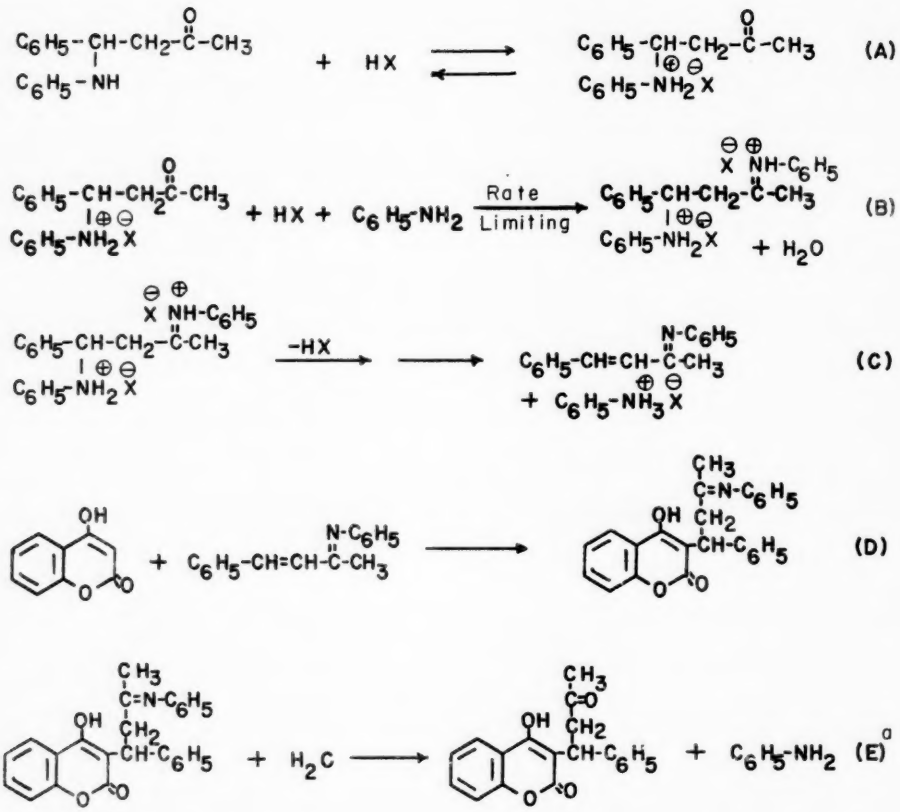
Additional evidence is provided for the above mechanism by a comparison of the catalytic effect of aniline with the tertiary bases dimethylaniline and triethylamine in the reaction of benzalacetone and 4-hydroxycoumarin to form warfarin (reaction 2). The data are in Table 2.

With dimethylaniline (a weak base of comparable strength to that of aniline) the yield is very low, while triethylamine a much stronger base

---

11 Kinetic studies have shown that reaction 1 is second order with respect to 4-hydroxycoumarin and first order with respect to both β-anilinobenzylacetone and aniline. These details will appear in a journal of the American Chemical Society.[3]

12 R. Adams and W. Reifschneider, Bull Soc. Chim. Fr. 49 (1958). The words are (bottom of column right) "Aliphatic molecules containing the $\rangle C=C-C=N-$ conjugation do not undergo 1,4-addition of active methylene compounds loc.cit. (57)." The emphasis is ours.



[a] At present it is not known whether step (E) occurs chiefly in the reaction mixture or during the isolation procedure.

catalyzes the formation of warfarin though to a lesser extent than aniline. It is well accepted that the role of triethylamine in the Michael reaction is that of a general base catalyst which removes the proton from the Michael donor and the activity of such a catalyst is a function of its base strength.[4b] Since aniline (a weak base) is more effective than triethylamine an alternate pathway is indicated. This suggests that in the presence of aniline benzalacetone anil is formed <u>in situ</u> which reacts with 4-hydroxycoumarin to

1960

TABLE 2[a].

The catalytic effect of aniline and the tertiary bases dimethylaniline and triethylamine in the production of warfarin from 4-hydroxycoumarin and benzalacetone

Base	Base (moles/l.)	Benzalacetone (moles/l.)	4-Hydroxy-coumarin (moles/l.)	Warfarin (% yield)
Aniline	0.67	0.67	1.0	94
Dimethylaniline	0.67	0.67	1.0	less than 4
Aniline	0.315	0.315	0.315	37
Triethylamine	0.315	0.315	0.315	19

[a] Each reaction was done in refluxing dioxane for 60 minutes.

form warfarin.

The scope of the above mechanism as it applies to the Michael reaction is now under investigation here.

Acknowledgements - We are indebted to Professors E.L. King, W.S. Johnson and A.L. Wilds of the University of Wisconsin's Department of Chemistry, and also to L.D. Dibble, Esq., of Adams, Forward and McLean, Washington,4, D.C., for counsel. This study was made possible by funds from the Wisconsin Alumni Research Foundation through Mr. Ward Ross, its General Manager, and the Research Committee of our Graduate School. We would welcome comment on this report. If it is favorable, send us a letter. If the reverse - send your comments to Tetrahedron Letters or elsewhere (K.P.L.).

Tetrahedron Letters No.13, pp. 30-33, 1960. Pergamon Press Ltd. Printed in Great Britain.

KATALYSIERTE HOMOLOGISIERUNG CYCLOALIPHATISCHER KETONE MIT DIAZOMETHAN

Eugen Müller, Martin Bauer* und Wolfgang Rundel

Chemisches Institut der Universität Tübingen

(Received 14 May 1960)

DURCH das Erscheinen der Mitteilung von Johnson et al. in Tetrahedron Letters[1] über eine neue Reaktion von Diazomethan mit α-β-ungesättigten Ketonen, sehen wir uns veranlaßt, in dieser Zeitschrift über das von uns seit längerem bearbeitete Gebiet der katalysierten Homologisierung cycloaliphatischer und aliphatischer Ketone näher zu berichten.[2]

Wir begannen unsere Versuche zur katalytischen Beeinflussung der Reaktion von Carbonylverbindungen mit Diazomethan auf Grund unserer Beobachtungen über die Katalysierbarkeit der Methylierung von Alkoholen[3] und konnten so, zunächst mit Borfluorid als Katalysator, eine bequeme Homologisierung der cycloaliphatischen Ketone erreichen.

Die Homologisierungsreaktion führten wir vom Cyclohexanon ausgehend schrittweise bis zum Cyclopentadecanon durch. Als Hauptprodukt wird dabei

---

* M. Bauer, Diplomarbeit, Universität Tübingen, September 1959.

1 W.S. Johnson, M. Neeman und S.P. Birkeland, Tetrahedron Letters No. 5, 1 (1960).

2 E. Müller, M. Bauer und W. Rundel, Z. Naturf. 15b, 268 (1960).

3 E. Müller und W. Rundel, Angew. Chem. 70, 105 (1958). E. Müller, M. Bauer und W. Rundel, Z. Naturf. 14b, 209 (1959).

1960

stets das nächst höhere Homoketon erhalten, daneben bilden sich in kleineren und abnehmenden Mengen die höheren Homologen, sowie etwas Polymethylen. Epoxyde lassen sich bei unserer Reaktion nicht nachweisen. Tabelle 1 gibt einen Überblick über die bei den einzelnen Reaktionsschritten erhaltenen Ausbeuten an homologen Ketonen. Weitere Versuche ergaben dann, daß sich

TABELLE 1

Ausgangsketon	mMol CH_2N_2* je 100 mMol Keton	Ausbeute an homologen Ketonen in %		
C_n		C_{n+1}	C_{n+2}	C_{n+3}
6	120	58	8,5	
	140	57	17	
	160	41	22,6	
7	135	49,6	16	
	150	49	14	
8	160	44	17	
	180	46		
9	150	42,2	6	
	165	44,5	7	
	180	43,7	7,2	
10	170	24,5	3,3	
	190	25,6	3,6	
11	180	13,3	3,2	
12	160	26,4	8	5,5
	270	21,4	7,8	9
	360	23	8,6	10
13	180	16,7	16.4	2,5
14	200	28,5	7,9	

* ca. 0,6 m ätherische Lösung.

außer Borfluorid auch zahlreiche andere Lewissäuren, z.T. noch viel vorteilhafter als Katalysatoren verwenden lassen. So lassen sich beispielsweise durch Zugabe entsprechender Mengen Diazomethan wahlweise die um 2 oder noch mehr CH_2 - Gruppen in einem Reaktionsschritt erweiterten Homologen zum Hauptprodukt der Reaktion machen. Die Polymethylenbildung kann man praktisch völlig unterdrücken. Tabelle 2 gibt einen Überblick über einen Teil der diesbezüglichen Versuche, die am Cyclooctanon durchgeführt wurden und zu den auf anderem Wege nur schwer zugänglichen Ringketonen mittlerer Größe (C_9-bis C_{11}-Ringketon) führen.

TABELLE 2

Katalysator	mMol CH_2N_2* je 50 mMol Keton	Ausbeute** in % an		
		C_9	C_{10}	C_{11}
$ZnCl_2$	60	25		
$AlCl_3$	70	40	20	
$AlBr_3$	60	49	11	
$AlBr_3$	120	24	43	17
$AlBr_3$	180	6	40	37
$Al(C_2H_5)_3$	120	15	40	25
$Al(C_4H_9)_3$	120	20	45	24
$Al(C_2H_5)_2Cl$	130	10	30	20
$Al(C_2H_5)_2Cl+TiCl_4$	120	30	35	15
$TiCl_4$	60	10		
$ZrCl_4$	120	30	44	10
HBF_4	60	33		

* ca. 0,6 m ätherische Lösung.

** gaschromatographisch bestimmt.

Andere Lewissäuren dagegen wie z.B. BCl_3, BBr_3, $B(OCH_3)_3$, $B(OCH_2CCl_3)_3$, $B(C_3H_7)_3$ oder $Al(O\text{-}i\text{-}C_3H_7)_3$ sind als Katalysatoren ungeeignet, da sie lediglich die Zersetzung des Diazomethans zu Polymethylen katalysieren. Wie schon früher angedeutet, scheint sich eine Entscheidung über die Brauchbarkeit eines Katalysators nach dem UV-spektroskopischen Verhalten der Ketonvorbande im System Keton + Katalysator treffen zu lassen.

Die Methode ist jedoch nicht auf die einfachen Cycloalkanone beschränkt, sie läßt sich auf Terpenketone, z.B. p-Menthon, anwenden. Trans-β-Dekalon liefert in einer Ausbeute von ca. 50% das bicyclische Homologe. Die Reaktion ist auch auf offenkettige Ketone übertragbar. So kann man z.B. aus dem Methyl-n-hexylketon als Hauptprodukte das Methylheptyl- und Methyl-octyl-keton erhalten.

Die Durchführung der Reaktion ist sehr einfach: Zur Lösung des Ketons in Äther wird eine geringe Menge Katalysator gegeben und unter Rühren und Eiskühlung ätherische Diazomethanlösung zugetropft. Durch Ausschütteln mit verdünnter Sodalösung oder Salzsäure läßt sich der Katalysator leicht entfernen. Das nach Abdestillieren des Äthers hinterbleibende Ketongemisch wird entweder gaschromatographisch oder in größerem Maßstab durch fraktionierte Destillation getrennt. Die Charakterisierung der erhaltenen Ketone erfolgte durch Analyse, sowie auf gaschromatographischem Wege und über die 2,4-Dinitrophenylhydrazone.

Die allgemeine Anwendung dieser Reaktion wurde bereits vor längerer Zeit zum Patent angemeldet.

Tetrahedron Letters No.13, pp. 34-35, 1960. Pergamon Press Ltd. Printed in Great Britain.

SYNTHESIS OF cis-10-HYDROXYDEC-2-ENOIC ACID

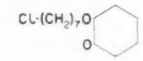
G. I. Fray, E. D. Morgan and Sir Robert Robinson

Research Laboratory, Shell Chemical Company Ltd., Egham, Surrey

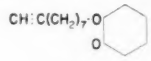
(Received 16 May 1960)

RECENTLY the synthesis of trans-10-hydroxydec-2-enoic acid, identical with the acid isolated from the 'royal jelly' of bees by Townsend and Lucas[1] was reported from this Laboratory.[2] We now describe the synthesis of the stereoisomer, cis-10-hydroxydec-2-enoic acid[3].

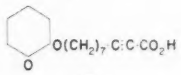
The starting material was pimelic acid, which by esterification, followed by reduction with lithium aluminium hydride, gave heptan-1,7-diol. The diol was converted into the 1,7-chlorohydrin by means of hydrochloric acid and cuprous chloride[4] and the hydroxyl group was then protected by formation of the tetrahydropyranyl ether (I) b.p. 92-95°/0.2 mm. (Found: Cl, 14.9. $C_{12}H_{23}O_2Cl$ requires Cl 15.1%).



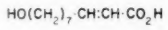
I



II



III



IV

Treatment of I with sodium iodide in acetone, followed by sodium acetylide in dimethyl formamide gave 9-2'-tetrahydropyranyloxynon-1-yne (II) b.p. 90-91°/0.3 mm. (Found: C,75.1; H, 10.7. $C_{14}H_{24}O_2$ requires

1 G. F. Townsend and C. C. Lucas, Biochem. J. 34, 1155 (1940)

2 G. I. Fray, R. H. Jaeger and Sir Robert Robinson, Tetrahedron Letters, No. 4, 15 (1960).

3 U.K. Patent Application No. 8576/60.

4 W. R. Coleman and W. G. Bywater, J. Amer. Chem. Soc. 66, 1821 (1944).

1960

C,75.0; H, 10.8%). Reaction of this acetylene with ethylmagnesium bromide under the special conditions described by Wotiz et al[5], followed by treatment with solid carbon dioxide, afforded the tetrahydropyranyloxy-acid (III) which was hydrolysed to 10-hydroxydec-2-ynoic acid, m.p. 72.0-73.0° (Found: C, 65.4; H, 8.7. $C_{10}H_{16}O_3$ requires C, 65.2; H, 8.8%). Its infra-red spectrum showed strong bands at 3.06 (O-H), 4.45 (C≡C), 6.02 (C=O) and 9.50μ (C-OH). Hydrogenation of this acetylenic acid over Lindlar's catalyst[6] gave a virtually quantitative yield of cis-10-hydroxydec-2-enoic acid (IV) m.p. 73.5-74.5° (Found: C, 64.4; H, 9.6. $C_{10}H_{18}O_3$ requires C, 64.5; H, 9.7%). The compound had an ultra-violet maximum at 2100Å, ε 12,450 and infra-red absorption bands at 2.90 (O-H), 5.92 (C=O), 6.15 (cis C=C), 9.52 (C-OH) and 12.3μ (cis CH=CH).

5 J. H. Wotiz, C. A. Hollingsworth and R. E. Dessy, J. Amer. Chem. Soc. 78, 1221 (1956)

6 H. Lindlar, Helv. Chim. Acta, 35, 446 (1952).

Tetrahedron Letters No.14, pp. 1-4, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

THE REACTION OF OZONE WITH ORGANIC HYDROPEROXIDES

D. Barnard, G. P. McSweeney and J. F. Smith

The British Rubber Producers Research Association,

Welwyn Garden City

(Received 22 March 1960; in revised form 25 April 1960)

OZONE and hydrogen peroxide are known to react with mutual deoxygenation and Taube and Bray[1] have demonstrated that a free radical chain process is involved with initiation by:-

$$H_2O_2 + O_3 \longrightarrow HO_2\cdot + HO\cdot + O_2$$

Organic hydroperoxides have now been shown to be destroyed by ozone in what is apparently a similar deoxygenation reaction. t-Butyl hydroperoxide, which gave the minimum of side reactions, was chosen for detailed study and Fig. 1 illustrates the ozone uptake curve for this peroxide in carbon tetrachloride solution at -25°. After ozone absorption had virtually ceased the colourless solution, in which droplets of water were visible, contained no peroxidic material reducible by stannous chloride. Analysis of the solution, after drying, by both infra-red spectrophotometry and gas-liquid chromatography (stationary phase dinonyl sebacate on acid-washed celite) gave results in excellent quantitative agreement. The major product was t-butanol accompanied by acetone and di-t-butyl peroxide. G.L.C. indicated the presence of only

---

[1] H. Taube and W.C. Bray, J. Amer. Chem. Soc. 62, 3357 (1940).

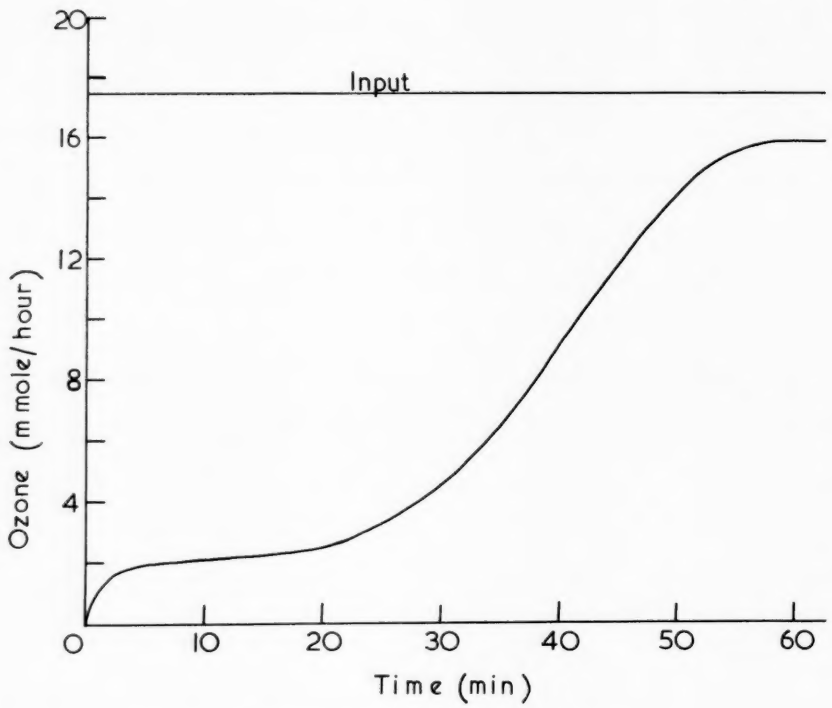


FIG. 1. Ozonolysis of Bu^tOOH (1.5 g) in CCl_4 (50 ml) at -25°C.

two other components, t-butyl chloride and a trace amount of an unidentified material. Table 1 shows the stoicheiometry of the reaction, water being independently estimated by the Karl Fischer technique.

TABLE 1

Products from the reaction of t-butyl hydroperoxide (1 mole) with ozone (0.51 mole)

Product	Bu^tOH	Bu^tOOBu^t	CH_3COCH_3	Bu^tCl	H_2O
Yield (mole)	0.68	0.079	0.10	0.042	0.264

1960

Of the original t-butyl groups 98 per cent are thus accounted for (acetone ≡ Bu^tO) but the active hydrogen balance is high (1.2 g atom) suggesting that part of the water has been derived by the further oxidation of t-butanol. Neither the products, nor their relative amounts, were altered significantly by changes in the ozone concentration or reaction temperature, although in very dilute ozone streams, loss of butanol and acetone in the effluent gas became noticeable.

Since carbon tetrachloride is stable to ozone under the reaction conditions but is readily attacked by reactive free radicals the formation of t-butyl chloride, which must result directly or indirectly from attack on solvent, implies that the ozone-hydroperoxide reaction involves such radicals. A reaction scheme, based largely on analogy with the hydrogen peroxide system, may therefore be postulated to account for the primary products observed, if not for their relative amounts.

$$ROOH + O_3 \longrightarrow RO_2\cdot + HO\cdot + O_2$$

$$HO\cdot + ROOH \longrightarrow RO_2\cdot + \underline{H_2O}$$

$$RO_2\cdot + O_3 \longrightarrow RO\cdot + 2O_2$$

$$RO\cdot + ROOH \longrightarrow \underline{ROH} + RO_2\cdot$$

$$2\,RO_2\cdot \longrightarrow \underline{ROOR} + O_2$$

As would be expected from this picture hydrocarbons used as solvent were extensively attacked. Thus a solution of t-butyl hydroperoxide in n-pentane absorbed many times more ozone than in carbon tetrachloride while the peroxide content decreased only slowly. This suggests an almost self-sustaining reaction in which hydroperoxide is generated by the radical-induced peroxidation of the solvent at approximately the same rate as it is

destroyed by ozone. If the ozonolysis were continued the n-pentane eventually became miscible with water. With cyclohexane as solvent cyclohexanone and adipic acid were identified as products of a similarly catalysed oxidation.

Hydroperoxides other than t-butyl, e.g. tetralyl and cyclohexyl, were similarly destroyed by ozone but apparently underwent a general radical attack at the same time to give highly oxygenated and complex products. Perbenzoic acid, as an example of an acyl hydroperoxide, was found to be stable to ozone at both -25° and 20° in carbon tetrachloride solution.

Ozone is well known to catalyse the autoxidation of hydrocarbons, presumably via hydrogen abstraction by atomic oxygen, and it might therefore be expected that subsequent interaction of ozone with the derived hydroperoxide or peroxy radicals would occur. It may be significant that Schubert and Pease[2] report that the major product of the interaction of isobutane with ozonized oxygen at 28° is t-butanol accompanied by a trace of acetone. A more surprising observation in view of the present results is that of Rindtorff and Schmitt,[3] who obtained cumyl hydroperoxide by the ozonization of cumene.

---

[2] C.C. Schubert and R.N. Pease, J. Chem. Phys. 24, 919 (1956).

[3] E. Rindtorff and K. Schmitt, Belg. Pat. 514, 128 (1952).

Tetrahedron Letters No.14, pp. 5-8, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

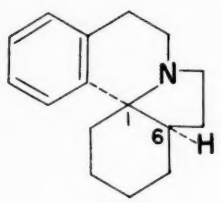
ZUR STEREOCHEMIE DER ERYTHRINANE

A. Mondon and K. F. Hansen[1]

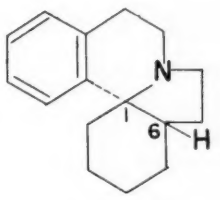
Institut für Organische Chemie der Universitat Kiel

(Received 25 May 1960)

DIE Stereochemie der Erythrinane, die durch Hydrierung der aromatischen Erythrina-Alkaloide oder durch Totalsynthese gewonnen werden, ist noch wenig erforscht. Nach der Theori können zwei Razemate auftreten, die sich vom 1.6-cis- und 1.6-trans-Erythrinan ableiten:



1,6—*cis*—



1,6—*trans*—

Erythrinan

Eine wichtige Beziehung besteht zwischen dem Methyläther des Hexahydro-apoerysodins,[2] einem Umwandlungsprodukt der Alkaloide, und dem synthetischen 15.16-Dimethoxy-erythrinan,[3,4] die der gleichen sterischen Reihe angehören.[5]

---

[1] Auszug aus der Dissert. Univ. Kiel 1960.

[2] M. Carmack, B.C. McKusick u. V. Prelog, Helv. Chim. Acta. 34, 1601 (1951).

[3] B. Belleau, Chem. & Ind. 410 (1956); Canad. J. Chem. 35, 651 (1957).

[4] A. Mondon, Angew. Chem. 68, 578 (1956); Chem. Ber. 92, 1461 (1959).

[5] V. Boekelheide, J. Amer. Chem. Soc. 81, 3955 (1959).

Aus Modellbetrachtungen an den natürlichen Alkaloiden hat Prelog[6] geschlossen, dass in ihren hydrierten Abkömmlingen, zu denen auch die oben genannte Verbindung gehört, wahrscheinlich trans-verknüpfte Erythrinane vorliegen. Diese sinnvolle Zuordnung war bisher die Grundlage sterischer Betrachtungen.

Neue Untersuchungen haben jedoch gezeigt, dass die synthetischen Basen der Reihe des 1.6-cis-Erythrinans angehören. Diese Aussage stützt sich auf folgende Experimente.

In Analogie zu einer bereits veröffentlichten Synthese[7] wurde über das Enol-lactam I das Hydroxy-lactam II gewonnen, aus dem durch Behandlung mit konz. Schwefelsäure der pentacyclische Äther III entsteht. Diese Verbindung lässt sich im Modell[8] ohne wesentliche Verzerrung der Ringe aufbauen, wenn der Indolteil der Molekel cis-verknüpft ist und sein Sechsring in der Wannenform vorliegt.

Die Aufspaltung der Oxydbrücke des Äthers III gelingt mit Acetanhydrid-Toluolsulfonsäure[9] ohne Änderung der Konfiguration am C-Atom 6. Es werden nach der Verseifung die ungesättigten Hydroxy-lactame IV und V isoliert, die bei ihrer Hydrierung die gesättigte Verbindung VI liefern. Sie ist identisch mit dem schon früher dargestellten Hydrierungsprodukt vom Schmp. 161° aus dem Enol-lactam IX.[7]

Die Hydroxy-Gruppe von VI lässt sich über das Tosylat und Iodid durch

---

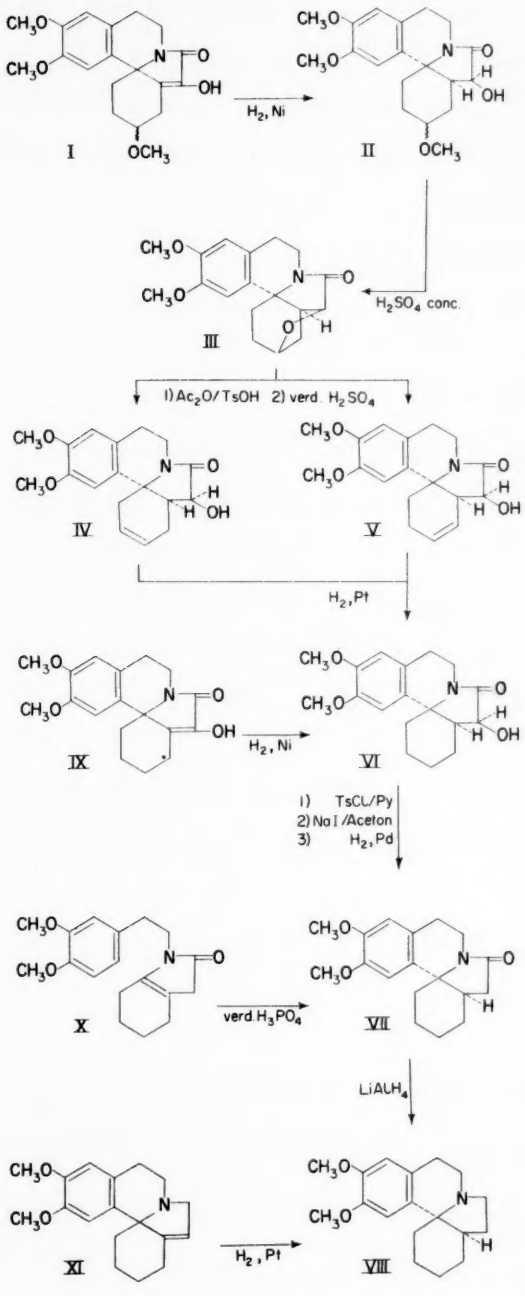
[6] V. Prelog, Angew. Chem. 69, 33 (1957).

[7] A. Mondon, Angew. Chem. 70, 406 (1958); Liebigs Ann. 628, 123 (1959).

[8] Dreiding-Stereomodelle, W. Büchi, Flawil (Schweiz).

[9] Zur Methode vgl. C. Djerassi, O. Halpern, G.R. Pettit u. G.H. Thomas, J. Org. Chem. 24, 1 (1959).

1960


I
II
III
IV
V
VI
VII
VIII
IX
X
XI
H_2, Ni
H_2SO_4 conc.
1) Ac_2O/TsOH 2) verd. H_2SO_4
H_2, Pt
1) TsCL/Py
2) NaI/Aceton
3) H_2, Pd
verd. H_3PO_4
$LiAlH_4$

anschliessende Reduktion leicht entfernen. Das Reaktionsprodukt VII ist wiederum bekannt und identisch mit dem Lactam vom Schmp. 118°, das durch Ringschluss z.B. aus der Vorstufe X erhalten wird.[10] Da von VII aus die Brücke über das 15.16-Dimethoxy-erythrinan zum Hexahydro-apoerysodin-methyl-äther schon geschlagen ist, müssen diese Basen - entsprechend VIII - als Derivate des 1.6-cis-Erythrinans formuliert werden. Schon früher wurde gefunden, dass die Base VIII auch bei der Hydrierung der ungesättigten Base XI entsteht.[7]

Kürzlich haben Prelog et al.[11] auf einem ganz anderen Weg für das synthetische 15.16-Dimethoxy-erythrinan-ol-(3) ebenfalls die 1.6-cis-Struktur bewiesen. Da auch das von Belleau[12] zuerst dargestellte "Erythrinan" nach unserer Untersuchung das 1.6-cis-Erythrinan ist, fügen sich alle Ergebnisse harmonisch zusammen. Das Gesamtbild lässt erkennen, dass bei den bekannten Totalsynthesen und durch Hydrierung stets cis-verknüpfte Erythrinane gebildet werden.

trans-Erythrinane sind nach unseren Erfahrungen schwer zugänglich, wir sind damit beschäfttigt, die Eigenschaften dieser Verbindungen näher kennen zu lernen.

Unser Dank gilt der Research Corporation New York und dem Fonds der Chemischen Industrie, die uns Mittel zur Durchführung dieser Arbeit zur Verfügung gestellt haben.

---

10 A. Mondon, Chem. Ber. 92, 1472 (1959).

11 V. Prelog, A. Langemann, O. Rodig u. M. Ternbah, Helv. Chim. Acta 42, 1301 (1959).

12 B. Belleau, J. Amer. Chem. Soc. 75, 5765 (1953).

Tetrahedron Letters No.14, pp. 9-12, 1960. Pergamon Press Ltd. Printed in Great Britain.

A NOVEL PEPTIDE SYNTHESIS

M. Zaoral and Z. Arnold

Dept. of Organic Synthesis,

Inst. of Organic Chemistry & Biochemistry,

Czechoslovak Academy of Science, Prague

(Received 25 May 1960)

IT has recently been shown by one of us (Z.A.) that N,N-dimethylformamide gives with carbonyl chloride an immonium chloride of the structure $\left[(CH_3)_2N{:}CH.Cl\right]^+ Cl^-$ which has been successfully applied as a reagent in the Vilsmeier-Haack aldehyde synthesis[1-3]. We have now been able to show that this compound is also an effective reagent for the synthesis of peptide bonds.

The reaction is carried out by treating one mole of the protected amino-acid or peptide with one mole of reagent in suitable solvent (e.g. chloroform, dichloromethane, dimethylformamide) with cooling (-5 to -10°) and adding the reaction mixture to a cooled (0°) solution of an amino-acid ester or peptide ester hydrochloride (one mole) containing three moles of a tertiary base. The reaction can be performed at temperatures as low as -70°.

Peptide derivatives synthesised in this way are listed in the Table. The results indicate that no racemisation took place when S-benzyl-N-benzyl-

---

[1] Z. Arnold and F. Šorm, Chem. listy 51, 1082 (1957); Coll. Czech. Chem. Comm. 23, 452 (1958).

[2] Z. Arnold, Chem. listy 52, 2013 (1958); Coll. Czech. Chem. Comm. 24, 4048 (1959).

[3] Z. Arnold and F. Šorm, Czechoslovak Patent 90,045 (1956).

TABLE

Product	Yield percent	M.p.
Phthaloylglycylglycine ethylester	86	194° [4]
Toluene-p-sulphonyl-L-leucylglycine methyl ester	78	116-117°
Benzyloxycarbonylglycylglycine methyl ester	77	66-67° [5]
S-Benzyl-N-benzyloxycarbonyl-L-cysteinylglycine methyl ester	80	106-107° [a]
S-Benzyl-N-benzyloxycarbonyl-L-cysteinylglycine ethyl ester	74	99-100° [b, 6]
N^{α}-Benzyloxycarbonyl-N^{ε}-toluene-p-sulphonyl-L-lysylglycine ethyl ester	75	153-154° [7]
N^{α}-(Benzyloxycarbonyl-L-prolyl)-N^{ε}-toluene-p-sulphonyl-L-lysylglycine ethyl ester [c]	88	151-152° [7]

[a] $[\alpha]_D^{23}$ -26.4 ± 0.5° (c 6, glacial acetic acid).

[b] $[\alpha]_D^{23}$ -26,8 ± 0.5° (c 6, glacial acetic acid); the literature[6] gives $[\alpha]_D^{20}$ -26.8° (c 6, glacial acetic acid).

[c] From benzyloxycarbonyl-L-proline and the dipeptide ethyl ester hydrobromide.

---

[4] R.A. Boissonnas, Helv. Chim. Acta 34, 874 (1951).

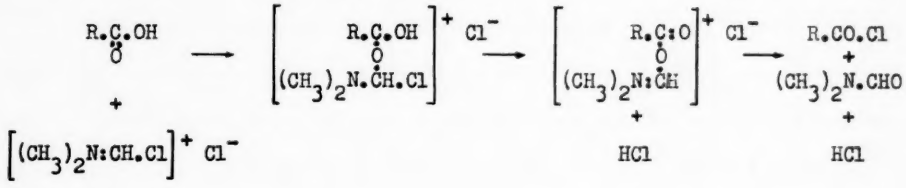
[5] N.F. Albertson and F.C. McKay, J. Amer. Chem. Soc. 75, 5323 (1953).

[6] S. Goldschmidt and Ch. Jutz, Chem. Ber. 86, 1116 (1953).

[7] R. Roeske, F.H.C. Stewart, R.J. Stedman and V. du Vigneaud, J. Amer. Chem. Soc. 78, 5883 (1956).

oxycarbonyl-L-cystein was used as the carboxyl component, but the synthesis of acetyl-L-leucylglycine ethyl ester (cf. 8) by the same procedure (-10°) was accompanied by extensive racemisation.

The way in which the carboxyl group is activated in this reaction has not so far been fully elucidated. In principle, the following reaction sequence may be envisaged:



The last stage of this reaction sequence is formulated as the reverse of the reaction between an acyl chloride and dimethylformamide[9]. The acyl chloride may in fact be isolated from the reaction mixture in suitable cases (e.g. phthaloylglycine) (cf. also 10). Neverthless it is possible that, at any rate at low temperatures, some of the postulated intermediates actually reacts as the species with an activated carboxyl group.

---

[8] M.B. North and G.T. Young, Chem. & Ind. 1597 (1955); M.B. North, N.A. Smart and G.T. Young, Abstracts Proc. 19th Internat. Congr. Pure and Appl. Chem. Paris 1957 Vol. II, p. 238.

[9] H.K. Hall, J. Amer. Chem. Soc. 78, 2717 (1956).

[10] H.H. Bosshard, R. Mory, M. Schmid and H. Zollinger, Helv. Chim. Acta 42, 1653 (1959).

The structural similarity between $\left[(CH_3)_2N{:}CH.Cl\right]^+ Cl^-$ and the dimethylformamide-SO_3 complex[11] prompts the question whether the mechenism of peptide synthesis with the latter reagent[12,13] is analogous to that of the synthesis described here. Indeed this is a plausible alternative to the mechanism originally proposed[12,13] for the formation of the intermediate acyl sulphate, but further experimental evidence would be required to distinguish between them[14].

Since the reagent is readily accessible and stable in chloroform solution, the reaction conditions mild, the procedure simple and the yields generally high we believe that the new method may prove convenient, especially for the synthesis of relatively simple peptides on a large scale.

We wish to thank Academician F. Šorm for his support of this work.

---

[11] S. Coffey, G.W. Driver, D.A.W. Fairweather and F. Irving, Brit. Patents 610,117 (1948) and 642,206 (1950).

[12] G.W. Kenner and R.J. Stedman, J. Chem. Soc. 2069 (1952).

[13] D.W. Clayton, J.A. Farrington, G.W. Kenner and J.M. Turner, ibid. 1398 (1957).

[14] We are indebted to Professor Kenner for discussion on this point.

Tetrahedron Letters No.14, pp. 13-18, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

STRUCTURE OF CUCURBITACIN B

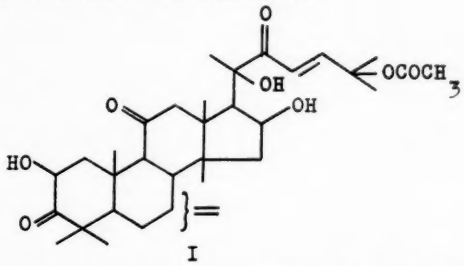
A. Melera, M. Gut, and C.R. Noller

Department of Chemistry and Chemical Engineering,

Stanford University, Stanford, California

(Received 11 May 1960)

STRUCTURE I has been proposed for cucurbitacin B.[1] We wish to report the results of experiments which provide evidence against this structure and suggest alternative structures.



I

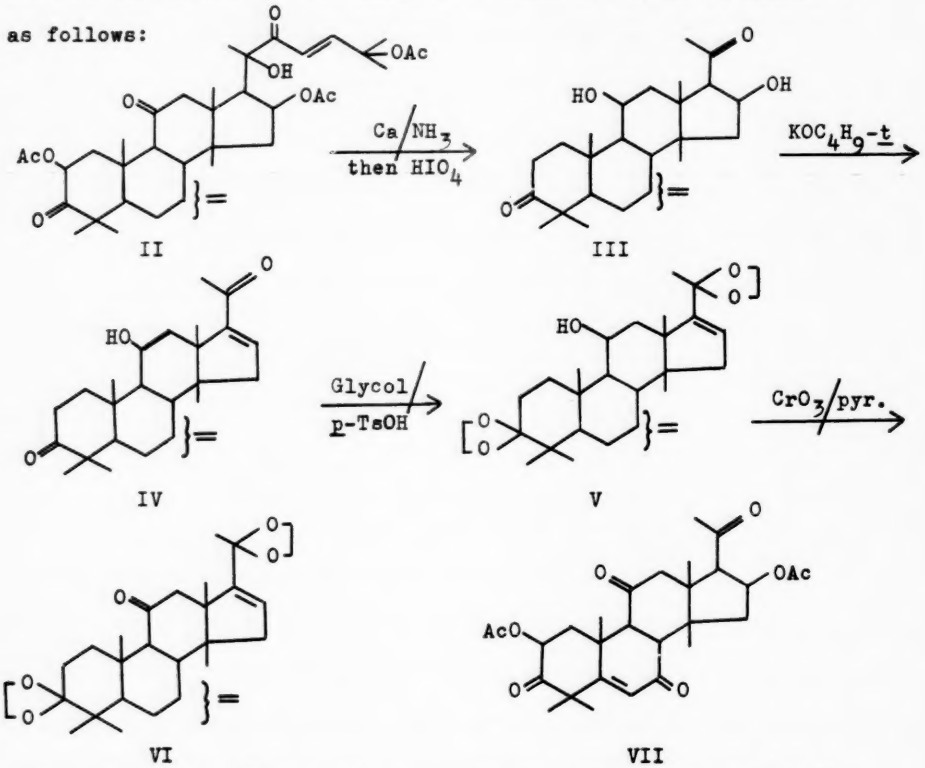
Optical rotatory dispersion curves have been reported for compounds having carbonyl groups in various positions of the steroid and tetracyclic and pentacyclic triterpene nuclei and such curves have been correlated with structure.[2] Hence the rotatory dispersion curve of a derivative of cucurbitacin B in which all of the carbonyl

---

[1] D. Lavie, Y. Shvo, D. Willner, P.R. Enslin, J.M. Hugo and K.B. Norton, Chem. and Ind. (London), 951 (1959).

[2] C. Djerassi, Optical Rotatory Dispersion. McGraw Hill, New York, 1960.

groups except that which is hindered are either eliminated or masked should provide information concerning the location of the hindered group. To prepare such a compound, a series of reactions was carried out, which, on the basis of formula I, may be represented as follows:



Acetylated fabacein[3] as well as acetylated cucurbitacin B was used for the preparation of compound III. Obviously the above reactions apply also for other possible positions of the hindered carbonyl group and of the unreactive double bond. The physical and analytical

---

[3] W. Schlegel and C.R. Noller, Tetrahedron Letters No. 13, p. 16 (1959).

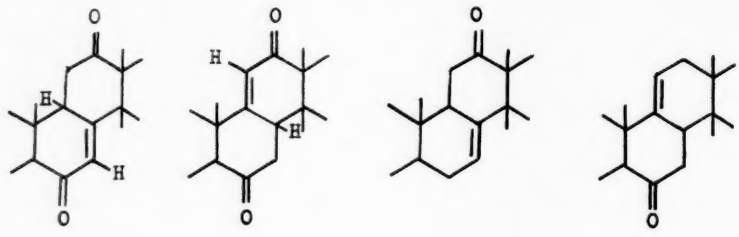
data (C, H, O) of the products are: III, m.p. 200-201°; IR 2.80, 2.90, 5.86; Calcd. for $C_{24}H_{36}O_4$: 74.19, 9.34, 16.47; Fd.: 74.47, 8.95, 16.73. IV, m.p. 221-222°; IR 2.86, 5.88, 6.00, 6.28; UV 244 (8600); Calcd. for $C_{24}H_{34}O_3$; 77.80, 9.25, 12.96; Fd.: 77.48, 9.25, 12.84. V, m.p. 195-197°; IR 2.78, 2.86, 6.21; Calcd. for $C_{28}H_{42}O_5$: 73.32, 9.23, 17.44; Fd.: 73.14, 9.07, 17.93. VI, m.p. 215-216°; IR 5.91, 6.21; Calcd. for $C_{28}H_{40}O_5$: 73.65, 8.83, 17.52; Fd.: 73.48, 8.96, 17.58.

These reactions in themselves gave useful information. For example an attempt to eliminate the carbonyl group from VI by the usual Huang-Minlon procedure failed, and only unchanged VI was recovered. Hence if the carbonyl group is at C-11, the double bond must be at the 5,6 position. If it were at the 7,8 position, it would have migrated into conjugation with a carbonyl group at C-11 under the conditions of the Huang-Minlon procedure.

A double bond at the 5,6 position and carbonyl at C-11 would require structure VII for ketone A.[4] However, the 60-mc NMR spectrum of ketone A has two distinct peaks at -375 and -378 cps using deuterochloroform as solvent and tetramethylsilane as an internal reference. The splitting of the band in this region indicates interaction of the proton on the conjugated double bond with a second nearby proton which can be accounted for by either partial structure VIII or IX but not by structure VII, and suggests partial structure X or XI for cucurbitacin B.

---

[4] A. Melera, W. Schlegel and C.R. Noller, J. Org. Chem. 24, 291 (1959).



VIII IX X XI

That the double bond in cucurbitacin B is trisubstituted is indicated by weak absorption in the infrared at 12.1 μ (825 cm^{-1}) and a broad flat band in the NMR spectrum at -350 cps, the broadening being caused by the adjacent methylene group.

The rotatory dispersion curve of VI is positive with a maximum $[\alpha]_{322}$ +2813° and a minimum $[\alpha]_{275}$ -2062° (c = 0.089 in dioxane). The magnitude of these rotations, among compounds having only an oxo group in ring B or C, for which RD curves have been reported, is approached only by 6-oxocoprostane and its curve is negative, $[\alpha]_{312}$ -2240° and $[\alpha]_{270}$ +2695°.[5] The curves for VI and 6-oxocoprostane are practically mirror images, and suggest a mirror image relationship in structure and configuration,[6] i.e., structure XI for cucurbitacin B with the α configuration at C-10 and at C-5. However, chemical evidence for structure X recently

---

[5] C. Djerassi and W. Closson, J. Am. Chem. Soc. 78, 3768 (1956). The magnitude of the minimum given in the experimental part as $[\alpha]_{312}$ -224° is a misprint (Private communication from Dr. C. Djerassi).

[6] cf. W. Klyne, J. Chem. Soc. 2916 (1952).

has been obtained by D. Lavie and Y. Shvo.[7] On the basis of either structure X or XI, it is difficult to understand why ketone A (VIII or IX) did not oxidize further with chromium trioxide in acetic acid to the conjugated dienedione or why we have been unable to bring about the further oxidation of ketone A with mercuric acetate, cupric acetate, or selenium dioxide.

1960

We wish to report also that by a series of nine steps, compound IV has been converted into a product, m.p. 280-281°, IR 5.86, 5.88, 5.91, tetranitromethane test negative. This compound, if cucurbitacin B had structure I with a configuration corresponding to lanostane or euphane, should be identical with either 7,11,20-trioxohexanorlanostane or 7,11,20-trioxohexanoreuphane. The latter compound is eliminated because it melts at 229°.[8] A mixture of our product with 7,11,20-trioxohexanorlanostane, m.p. 281-282°,[9] melted at 245-255°.

Acknowledgments. We are indebted to Dr. E.J. Eisenbraun and Mrs. T. Nakano for determining the rotatory dispersion curve of compound IV, and to Dr. O. Jeger for samples of the lanostane and

---

[7] We wish to thank Dr. Lavie for a copy of a Communication submitted to Chemistry and Industry (London) in which this structure is proposed.

[8] M. Dünnenberger, Dissertation, Eidg. Tech. Hochschule, Zürich, 1955.

[9] W. Voser, M.V. Mijović, O. Jeger and L. Ruzicka, Helv. Chim. Acta 34, 1585 (1951), report an uncorrected melting point of 269-271°.

euphane derivatives. This work was supported in part by a research grant, RG-5076, from the National Institutes of Health, U.S. Public Health Service.

Tetrahedron Letters No.14, pp. 19-20, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

CYCLOPENTADIENYLTRIMETHYLTITANIUM

Umberto Giannini and Sebastiano Cesca

Istituto di Chimica Industriale del Politecnico di Milano

(Received 3 June 1960)

METALLORGANIC compounds of tetravalent titanium in which all the valences are saturated by organic groups have been isolated in the pure state only when two of the organic groups are cyclopentadienyl[1,2] or substituted cyclopentadienyl.[2]

The presence of the two cyclopentadienyl nuclei gives a particular stability to this class of metallorganic compounds. Thus, for instance, dicyclopentadienyldiphenyltitanium and dicyclopentadienyldimethyltitanium are not decomposed by water or by alcohols and are not oxidized when exposed to air.[1,2]

We have now prepared and isolated in the pure state a monocyclopentadienyl compound of tetravalent titanium in which all the valences are saturated by organic groups, corresponding to the formula $(C_5H_5)Ti(CH_3)_3$.

Reaction under nitrogen at -30°C of cyclopentadienyltitaniumtrichloride* (4 g, 18.2 millimoles) suspended in anhydrous diethylether (100 mls.) with lithium methyl (1.32 g, 60 millimoles) dissolved in

* $(C_5H_5)TiCl_3$ prepared by us according to R. D. Gorsich[3] showed, after crystallization from xylene, m.p. 210-213°C, contrary to previous indications.[3,4]

1 L. Summers, R. H. Uloth, A. Holmes, J. Amer. Chem. Soc. 77, 3604 (1955)

2 D.P. 1,037,443, 28/8/1958, Farbwerke Hoechst.

3 R. D. Gorsich, J. Amer. Chem. Soc. 80, 4744 (1958)

4 O. L. Sloan, W. A. Barber, J. Amer. Chem. Soc. 81, 1364 (1959)

80 ml of ether is accompanied by dissolution of the titanium compound to a yellow solution and precipitation of lithium chloride.

After about 2 hours the solvent is removed by evaporation and then the reaction product is sublimed at the room temperature/0.5 mm, and collected on a tube wall cooled to -70°C.

1.1 g of intensely yellow needle crystals* are thus isolated (Found: Ti, 30.4; Me,$^{(o)}$ 28.6; M,$^{(oo)}$ 165.4. $(C_5H_5)Ti(CH_3)_3$ requires Ti, 30.3; Me, 28.53%; M, 158.09).

(o) determined by measuring the volume of methane evolved on reaction with 2-ethylhexanol.

(oo) Cryoscopic in benzene.

A further purification of the product may be accomplished by recrystallization from pentane solutions at about -70°C.

Cyclopentadienyltrimethyltitanium kept under an inert atmosphere decomposes very slowly at temperatures near 0°C, and rapidly at temperatures higher than 40°C. It may be kept for a long time without significant decomposition when it is maintained at about -70°C.

Unlike $(C_5H_5)_2Ti(CH_3)_2$ and $(C_5H_5)_2Ti(C_6H_5)_2$, cyclopentadienyltrimethyltitanium quickly reacts with water and alcohols, with formation of methane, and is rapidly oxidized by air. Therefore this compound shows a reactivity similar to that of methyltitaniumtrichloride.[5] From this behaviour it is possible to deduce that, when only one cyclopentadienyl group is present in the molecule, the methyl groups are bound to titanium by means of bonds having a limited stability and a high reactivity, contrary to what happens in the case of dicyclopentadienyl derivatives.

---

5 D.B.P. 1,023,766, 16/12/1955, Farbwerke Hoechst; C. Beerman, H.Bestian, Ang. Chem. 71, 618 (1959).

* In which chlorine is absent.

Tetrahedron Letters No.14, pp.21-22, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

THE SYNTHESIS OF γ-FLUOROGLUTAMIC ACID

M. Hudlický

Research Institute for Pharmacy and Biochemistry

Prague, Czechoslovakia

(Received 30 May 1960)

SOME of the organic monofluorides show interesting properties as antimetalbolites. Thus fluorocitric acid has been recognized as an antimetabolite of citric acid in the Krebs cycle[1] and 5-fluorouracil as an antimetabolite for uracil in the synthesis of nucleic acids.[2] It was interesting to find out what an effect would produce the introduction of fluorine into the molecules of some amino acids. After some unsuccessful attempts to synthesize fluoroaspartic acid,[3] γ-fluoroglutamic acid has been prepared by the following sequence of reactions:

Ethyl α,α,β-tribromopropionate was converted by heating with mercurous fluoride and iodine to ethyl α,β-dibromo-α-fluoropropionate[4](I), b.p. 67-67.5°/ 3.2 mm, n_D^{20} 1.4810; (Found: C, 21.60%, H, 2.59%. Calc. for $C_5H_7Br_2FO_2$: C, 21.6%, H, 2.54%). Dehalogenation with zinc of ethyl α,β-dibromo-α-fluoro-

---

[1] R.H. Peters, Endeavour 13, 147 (1954).

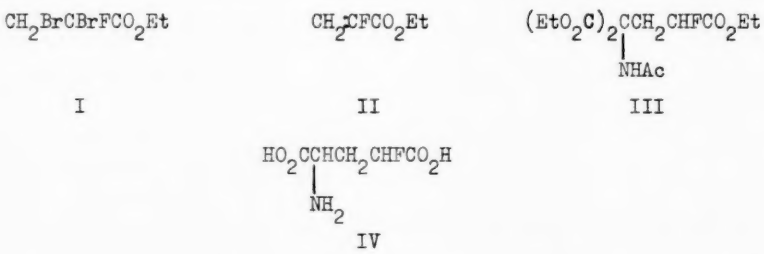
[2] M.P. Gordon and M. Staehelin, J. Amer. Chem. Soc. 80, 2340 (1958).

[3] M. Hudlický, Unpublished results.

[4] A.L. Henne, J. Amer. Chem. Soc. 76, 479 (1954).

propionate afforded 70% yield of ethyl α-fluoroacrylate (II), b.p. 110°/728 mm, n_D^{20} 1.3940; (Found: C, 50.68%, H, 6.12%. Calc. for $C_5H_7FO_2$: C, 50.85%, H, 5.98%). Michael addition of ethyl acetamidomalonate to ethyl α-fluoroacrylate in the presence of sodium ethoxide yielded 58-68% of ethyl 1-fluoro-3-acetamido-1,3,3-propanetricarboxylate (III), m.p. 103-104° (from ethanol); (Found: C, 50.51%, H, 6.57%, F, 5.95%, N, 4.05%. Calc. for $C_{14}H_{22}FNO_7$: C, 50.15%, H, 6.58%, F, 5.67%, N, 4.18%). Hydrolysis of the ester III by boiling with concentrated hydrochloric acid followed by the removal of chloride ions with silver oxide gave, after evaporation in vacuo, γ-fluoroglutamic acid (IV) in 50-60% yield.

γ-Fluoroglutamic acid separated from the aqueous solution as a white microcrystalline substance, melting at 184-186° with a slight decomposition. After crystallization from water the m.p. rose to 191-192° (when heating the sample in a sealed capillary starting at 150°). (Found: C, 35.97%, H, 4.99%. F, 11.71%, N, 8.64%. Calc. for $C_5H_8FNO_4$: C, 36.37%, H, 4.89%, F, 11.51%, N, 8.48%). R_F for the system butanol-acetic acid-water (4:1:5) was 0.05, for the system isopropanol - ammonium hydroxide - water (9:1:2) 0.14.(Glutamic acid had the respective R_F values 0.16 and 0.14). The reaction of γ-fluoroglutamic acid with ninhydrin produced a yellow color.



I II III

IV

The author wishes to express his thanks to Dr. O. Němeček, to Dr. J. Weichet, to Dr. K. Macek (for paper chromatography), and to V. Malý, J, Komancová, D. Aixnerová, J. Schmidtová, E. Dvořáková, V. Smídová and E. Vaníková (for the analyses).

Tetrahedron Letters No.14, pp. 23-26, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

CONFORMATION OF SOME 4-HYDROXYPIPERIDINES

M. Balasubramanian and (Miss) N. Padma

Department of Chemistry, Annamalai University,

Annamalainagar, India

(Received 1 June 1960)

ALTHOUGH a number of substituted 4-hydroxypiperidines are known,[1,2] a thorough study of the conformation of such compounds is limited to tropine and ψ-tropine.[3] Conformational analysis is made difficult in this type of compounds due to the flexibility of the heterocyclic ring. Baliah et al.[4] synthesized a number of 2,6-diaryl-4-piperidones. The bulky aromatic substituents in these compounds should restrict the ring to a single chair form, particularly when they are cis and occupy equatorial positions. The failure to resolve 1-methyl-2,6-diphenyl-4-piperidone has been ascribed to the cis relationship of the two phenyl groups.[5] The same configuration can be expected for similar

---

[1] A. Ziering and J. Lee, J.Org.Chem. 12, 911 (1947); and earlier papers; I.N. Nazarov, D.V. Sokolov and V.N. Rakcheeva, Izv.Akad.Nauk SSSR, Otdel.Khim.Nauk 80 (1954); Chem.Abstr. 49, 6248 (1955); and earlier papers.

[2] V. Baliah and A. Ekambaram, J.Indian Chem.Soc. 32, 274 (1955).

[3] W. Klyne, Progress in Stereochemistry Vol. 1, p. 80. Butterworths, London (1954).

[4] C.R. Noller and V. Baliah, J.Amer.Chem.Soc. 70, 3853 (1948); V. Baliah and V. Gopalakrishnan, J.Indian Chem.Soc. 31, 250 (1954); V. Baliah, V. Gopalakrishnan and T.S. Govindarajan, J.Indian Chem.Soc. 31, 832 (1954); V. Baliah, A. Ekambaram and T.S. Govindarajan, Curr.Sci. (India) 23, 264 (1954); V. Baliah and A. Ekambaram, Sci. & Cult. (India) 20, 193 (1954).

[5] R.E. Lyle and G.G. Lyle, J.Org.Chem. 24, 1679 (1959).

piperidones. The reduction of these compounds by the Meerwein - Ponndorf - Verley (MPV) method has been reported[2] to yield isomeric 4-hydroxypiperidines, designated as α- and β-forms. Assuming a chair conformation for the ring, the hydroxyl would be equatorial in one form and axial in the other. We report in this communication a study of the conformation of these hydroxy compounds.

The piperidones were reduced by (1) the MPV method, (2) sodium and n-butanol and (3) lithium aluminium hydride. The MPV method gave a mixture of α- and β-forms which were separated by chromatographic adsorption on alumina. The other two methods gave chiefly a single isomer, the α-form. This was also purified by chromatography. It may be noted that most of the compounds obtained by earlier workers[2,5] were not adequately pure.

Reduction of 2,6-diphenyl-4-piperidone, A by the MPV method gave Iα [m.p. 123-124°, lit.[2] 99-101°; ν cm^{-1} (CS_2) 3546 (free OH), 3247 (bonded OH)]. (Found: C, 81.10; H, 7.49. $C_{17}H_{19}NO$ requires C, 80.61; H, 7.56.) and Iβ [m.p. 139-140°, lit.[2] 135-136°; ν cm^{-1} (CS_2) 3571 (free OH)]. (Found: C, 80.46; H, 7.12. $C_{17}H_{19}NO$ requires C, 80.61; H, 7.56). 1-Methyl-2,6-diphenyl-4-piperidone, B gave IIα [m.p. 163-164°, lit.[5] 170-172.5°; ν cm^{-1} (CS_2) 3584 (free OH), 3205 (bonded OH)]. (Found: C, 81.14; H, 7.60. $C_{18}H_{21}NO$ requires C, 80.85; H, 7.92) and IIβ [m.p. 170-171°, lit.[5] 155-156°; ν cm^{-1} (CS_2) 3560 (free OH)]. (Found: C, 81.30; H, 7.70. $C_{18}H_{21}NO$ requires C, 80.85; H, 7.92). Repeated chromatography of IIα on alumina did not improve the melting point. Lyle and Lyle[5] report the product from the MPV reduction melting at 155-156° as a pure isomer but it should be a mixture of the two forms. Our product from the MPV method melted at 140-150° before separation of the two forms. Reduction of A and B with sodium and n-butanol or with $LiAlH_4$ furnished a single isomer

in each case, Iα and IIα respectively. Heating of Iβ or IIβ with sodium ethoxide in refluxing xylene gave the corresponding α-form in high yield. The alcohols IIα and IIβ were also obtained by the methylation of Iα and Iβ with methyl iodide and potassium carbonate in refluxing acetone.

Reduction of 3,5-dimethyl-2,6-diphenyl-4-piperidone, C by the MPV method yielded chiefly IIIβ [m.p. 111-112°, lit.[2] 110-111°; ν cm^{-1} (CS_2) 3560 (free OH)]. (Found: C, 81.43; H, 8.37. $C_{19}H_{23}NO$ requires C, 81.10; H, 8.24) and a small amount of IIIα [m.p. 132-133°, lit.[6] 133-134°; ν cm^{-1} (CS_2) 3571 (free OH), 3247 (bonded OH)]. (Found: C, 80.93; H, 7.78. $C_{19}H_{23}NO$ requires C, 81.10; H, 8.24). Whereas reduction with sodium and n-butanol furnished only IIIα, reduction with $LiAlH_4$ gave IIIα along with a small quantity of IIIβ. Similar results were obtained with 1,3,5-trimethyl-2,6-diphenyl-4-piperidone, D. The MPV method gave IVα [m.p. 133-134°, lit.[2] 126-128°; ν cm^{-1} (CS_2) 3571 (free OH), 3333 (bonded OH)]. (Found: C, 81.19; H, 9.01. $C_{20}H_{25}NO$ requires C, 81.32; H, 8.53) and IVβ [m.p. 99-100°, lit.[2] 90-92°; ν cm^{-1} (CS_2) 3571 (free OH)]. (Found: C, 81.30; H, 8.66. $C_{20}H_{25}NO$ requires C, 81.32; H, 8.53), sodium and n-butanol gave only IVα and $LiAlH_4$ yielded a mixture consisting chiefly of IVα. Methylation of IIIα and IIIβ with CH_3I gave IVα and IVβ respectively. Equilibration of either the α- or the β-form of III or IV with sodium ethoxide in xylene gave unchanged starting materials and under more severe conditions (potassium t-butoxide in decalin at 200°) extensive decomposition occurred.

Reduction of unhindered cyclic ketones with $LiAlH_4$ or with sodium and alcohol has been shown to yield predominantly equatorial alcohols.[7,8] It is

---

[6] E.A. Mailey and A.R. Day, J. Org. Chem. 22, 1061 (1957).

also well known[7] that equilibration of secondary alcohols with alkali gives a mixture consisting predominantly of thermodynamically the more stable equatorial alcohol. These facts indicate that the hydroxyl groups in Iα and IIα are equatorial and those in Iβ and IIβ are axial. Similar conformations follow for IIIα, IVα, IIIβ and IVβ also, though they could not be subjected to epimerization. Such an assignment of conformation is consistent with their infra-red spectra and their behaviour towards adsorption on alumina. The equatorial alcohol is more strongly adsorbed on alumina than the axial alcohol.[7] In the present work the β-forms were eluted first, thus suggesting that the hydroxyl in them has axial disposition. Infra-red absorption of the α-forms gives two bands in the region 3600-3200 cm^{-1}, a sharp band due to the free hydroxyl group and a broad band due to the bonded hydroxyl, whereas the β-forms give a single sharp band. Hydrogen bonds are known to form more readily when the hydroxyl is equatorial, since it is then sterically more accessible.[9]

The authors are grateful to Professor V. Baliah for his interest and encouragement. Our thanks are also due to Professor T.R. Govindachari, Presidency College, Madras, for the infra-red measurements. One of us (N.P.) thank the University Grants Commission for the award of a scholarship.

---

[7] D.H.R. Barton, J. Chem. Soc. 1027 (1953).

[8] W.G. Dauben, E.J. Blanz, Jr., J. Jiu and R.A. Micheli, J. Amer. Chem. Soc. 78, 3752 (1956).

[9] E.E. Pickett and H.E. Ungnade, J. Amer. Chem. Soc. 71, 1311 (1949); E.G. Peppiatt and R.J. Wicker, J. Chem. Soc. 3122 (1955); E.L. Eliel, J. Chem. Educ. 37, 130 (1960).

1960

Tetrahedron Letters No.15, pp. 1-4, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

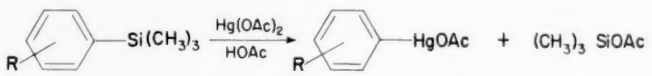
SUBSTITUENT EFFECTS IN AROMATIC SUBSTITUTION

Robert A. Benkeser, Thomas V. Liston and Garth M. Stanton

Department of Chemistry, Purdue University, West Lafayette, Indiana

(Received 1 June 1960)

RECENTLY[1] we reported that mercuridesilylation [equation (I)] constitutes a



I

convenient method for determining the reactivity of a particular ring position in an aromatic system. The mercuriacetate enters the position occupied by the trimethylsilyl group at a convenient rate to measure.

We are hereby reporting the results of an application of this method to a study of the electrical effects of alkyl groups on an aromatic ring (equation I, where R = m and p-CH_3, C_2H_5, i-C_3H_7 and t-C_4H_9). As will be noted from Table 1, the meta alkyl series shows a gradual increase in rate of cleavage which is readily explainable in terms of the gradually increasing inductive effect of the meta alkyl substituent. Surprisingly however, the para alkyl series also shows the same gradual increase in rate. This becomes

[1] R.A. Benkeser, D.I. Hoke and R.A. Hickner, J.Amer.Chem.Soc. 80, 5294 (1958).

[2] For other exceptions see: W.M. Lauer, G.W. Matson and G. Stedman, J.Amer.Chem.Soc. 80, 6437 (1958); H. Cohn, E.D. Hughes, M.H. Jones and M.G. Peeling, Nature, Lond. 169, 291 (1952); C. Eaborn and R. Taylor, Chem. & Ind. 949 (1959).

TABLE 1.

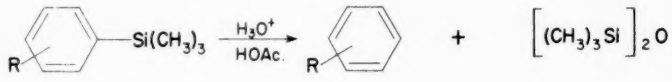
Cleavage of Alkylphenyltrimethylsilanes by Mercuric Acetate in Glacial Acetic Acid at 25° (a)

Alkyl Group	k/k_H (b)
m-CH_3	2.51
m-i-C_3H_7	3.96
m-t-C_4H_9	5.50
p-CH_3	10.60
p-C_2H_5	11.50
p-i-C_3H_7	12.00
p-t-C_4H_9	14.00

(a) The solution was 0.1788 M in mercuric acetate and 0.017 M in silane.

(b) These rates are relative to the unsubstituted compound, phenyltrimethylsilane.

one of the rare electrophilic substitution wherein p-alkyl groups do not activate in the Baker - Nathan (hyperconjugative) order.[2] On the other hand, preliminary results of protodesilylation [equation (II)] from our Laboratory indicate that p-alkyl groups follow the Baker - Nathan order.



II

1960

In view of recent disclosures regarding the influence of solvation upon the electron release of alkyl groups, one is tempted to explain these anomalous results in terms of a solvent effect.[3-6] This becomes a particularly attractive explanation when one considers that protodesilylations, which follow the Baker - Nathan order, are routinely carried out in a highly polar medium (mineral acid in aqueous acetic acid), while the mercuridesilylations reported in Table 1 are carried out in a relatively non-polar medium (mercuric acetate in glacial acetic acid).

While solvation effects may indeed be the sole explanation for the anomalies observed, a second possibility exists which cannot be overlooked at this time. The mercuridesilylation reaction is one of low selectivity,[7] having an S_f factor of 0.63.[8] In terms of the Hammond[9] postulate, the transition state for mercurisesilylation will resemble the reactants, in that very little breaking of the carbon-silicon bond has occurred. Hence very little positive ion character is developed in the aromatic ring in the transition state, and hence there is very little demand upon the electron releasing properties of the para alkyl groups. An interesting corollary to

[3] See series of papers in Tetrahedron 5, 166 (1958).

[4] R.S. Mulliken, Tetrahedron 6, 68 (1959).

[5] W.A. Sweeney and W.M. Schubert, J.Amer.Chem.Soc. 76, 4625 (1954);and subsequent papers.

[6] R.A. Clement and J.N. Naghizadeh, J.Amer.Chem.Soc. 81, 3154 (1959).

[7] See L.M. Stock and H.C. Brown, J.Amer.Chem.Soc. 81, 5621 (1959) for leading references to this concept.

[8] The S_f factor for aromatic mercuration at 25° is 1.01. [H.C. Brown and C.W. McGary, Jr., J.Amer.Chem.Soc. 77, 2306 (1955)]. From these and other data, it would appear that reactions which involve the breakage of a carbon-silicon bond are uniformally less selective than the corresponding reaction involving a carbon-hydrogen bond breakage (e.g. mercuridesilylation and aromatic mercuration).

[9] G. Hammond, J.Amer.Chem.Soc. 77, 334 (1955).

this second explanation would be that mercuridesilylation rates should correlate more satisfactorily with Hammett's sigma constants than with Brown's σ^+ constants,[10] sonce the latter reflects resonance interactions to a greater extent than the former. We plan to check this point.

Acknowledgement - The authors are grateful to the National Science Foundation for a fellowship grant which made this work possible.

---

[10] H.C. Brown and Y. Okamoto, J.Amer.Chem.Soc. 79, 1913 (1957).

Tetrahedron Letters No.15, pp. 5-8, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

THE REACTION OF DIARYL TELLURIDES WITH VIC-DIBROMIDES

A NEW AGENT OF DEBROMINATION

M. de Moura Campos, N. Petragnani and C. Thomé

Department of Chemistry, Escola Politécnica, University of São Paulo, Brazil

(Received 2 June 1960)

THE fact that aryltellurides (I) are very easily transformed into the corresponding diaryl tellurium dihalides[1] (III) led us to study their reaction with ethylene bromides in order to obtain ethylenes (IV).

$$\underset{\text{(I)}}{\text{Ar-Te-Ar'}} + \underset{\text{(II)}}{\text{RCHBr-CHBrR'}} \longrightarrow \underset{\text{(III)}}{\text{Ar-Te(Br)(Br)-Ar'}} + \underset{\text{(IV)}}{\text{RCH=CHR'}}$$

Actually refluxing a solution of diphenyl telluride (I: Ar=Ar=C_6H_5) in ethylene bromide for about two hours the corresponding tellurium dibromide was obtained in good yield. Several diaryl tellurides (I) and vic-dibromides (II) were used and the compounds of type III and IV (when solids) obtained in these experiments have been identified by mixed melting point with authentic samples. The results are given in Table 1.

Performing the reaction of diphenyl telluride and ethylene bromide under mild conditions (gently refluxing during 30 min) the ethylene bis

---

[1] K. Lederer, Ber. 49, 334 (1916); K. Lederer, Ann. 391, 326 (1912); H. Rheinboldt and G. Vicentini, Ber. 89, 624 (1956).

diphenyl telluronium bromide (V) was obtained in 74% yield. (m.p. 259-263°; Found: Te, 33.7. $C_{26}H_{24}Br_2Te_2$ requires Te, 33.96). This compound is the first that contains two tellurium atoms in the same molecule.

$$2\ C_6H_5TeC_6H_5 + BrCH_2\text{-}CH_2Br \longrightarrow \underset{\displaystyle Br[(C_6H_5)_2Te}{\overset{\displaystyle CH_2\text{-}CH_2}{|\quad\quad|}}\ \underset{\displaystyle Te(C_6H_5)_2]Br}{}$$

(V)

A solution of compound V in ethylene bromide being vigorously refluxed gave rise to yellow crystals of diphenyl tellurium dibromide (m.p. 199-202°). The same transformation was observed when compound V was recrystallized from glacial acetic acid.

$$V \begin{cases} \longrightarrow BrCH_2\text{-}CH_2Br \longrightarrow 2(C_6H_5)_2TeBr_2 + 2CH_2{=}CH_2 \\ \longrightarrow HOAc \longrightarrow (C_6H_5)TeBr_2 + CH_2\text{-}CH_2 + (C_6H_5)_2Te \end{cases}$$

Whether or not the telluronium bromides of type V are necessarily intermediate in these debromination reactions is under investigation.

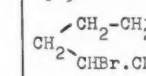
It was also shown that a solution of diphenyl telluride in allyl bromide heated at 180° in a sealed tube for 3 hr gives rise to a diphenyl tellurium dibromide and probably diallyl.

$$C_6H_5TeC_6H_5 + 2CH_2{=}CH\text{-}CH_2\text{-}Br \longrightarrow (C_6H_5)_2TeBr_2 + (CH_2{=}CH\text{-}CH_2)_2$$

No reaction occured when a mixture of n-butyl bromide and diphenyl telluride was heated in a sealed tube at 180° for two days. Under the same experimental conditions methyl iodide gave rise to the corresponding telluronium iodide. In this connexion it is interesting to point out

TABLE 1.

Reaction of Diaryl Tellurides with vic-Dibromides

Diaryl tellurides (I)		Vic-dibromides (II)	Solv.	temp.	Diaryl tellurium dibromides (III)		Yield %	Ethylenes (IV)	Yield %
Ar	Ar'				Ar	Ar'			
β-$C_{10}H_7$	p-CH_3O-C_6H_4	$BrCH_2$-CH_2Br	II	b.p.solv.	β-$C_{10}H_7$	p-CH_3O-C_6H_4	66	-	-
α-$C_{10}H_7$	p-CH_3O-C_6H_4	$BrCH_2$-CH_2Br	II	b.p.solv.	α-$C_{10}H_7$	p-CH_3O-C_6H_4	70	-	-
C_6H_5	C_6H_5	$BrCH_2$-CH_2Br	II	b.p.solv,	C_6H_5	C_6H_5	86	-	-
C_6H_5	C_6H_5	$C_6H_5CHBr.CHBrC_6H_5$	-	150°	C_6H_5	C_6H_5	85	$C_6H_5CH=CHC_6H_5$ (trans)	94[a]
C_6H_5	C_6H_5	$C_6H_5CHBr.CHBrCOOH$	-	110°	C_6H_5	C_6H_5	74	$C_6H_5CH=CHCOOH$	100[b]
C_6H_5	C_6H_5		II	b.p.solv.	C_6H_5	C_6H_5	84[c]	-	-
C_6H_5	C_6H_5	Dibromo cholesterol	xilene	b.p.solv.	C_6H_5	C_6H_5	77	Cholesterol	58[d]
C_6H_5	C_6H_5	Dibromo cholesterol	-	95°	C_6H_5	C_6H_5	71	Cholesterol	93[e]

[a] Crude product: recrystallization from ethanol m.p. 118-123°.

[b] Crude product: recrystallization from ethanol/water, m.p. 128-133°.

[c] Impure product.

[d] Crude product: rec.from glacial acetic acid then twice from ethanol/water, m.p. 146-149°.

[e] Very impure product: several rec. from different solvents, m.p. 133-146°.

[4] H. Rheinboldt and G. Vicentini, Ber. 89, 624 (1956).

that Lederer has shown that the reaction of methyl iodide[2] and α-bromo acids and esters[3] with tellurides, when performed at room temperature gives rise to the corresponding telluronium halides, but even at higher temperature debromination of the alkyl halide was never observed.

Since diaryl tellurides may be recovered quantitatively by treating the diaryl tellurium dihalides with sodium sulphite[5] they are suitable debromination agents.

The authors are greatly indebted to Professor H. Hauptmann for reviewing the manuscript and also to the Rockefeller Foundation, New York, and the Conselho Nacional de Pesquisas, Rio de Janeiro, for financial support.

---

[2] K. Lederer, Ann. 399, 262 (1913).

[3] K. Lederer, Ber. 46, 1362 (1913).

[4] See Table 1 on page 7.

[5] L. Reichel and E. Kirschbaum, Ber. 76, 1105 (1943).

Tetrahedron Letters No.15, pp. 9-14, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

THE DETERMINATION OF CARBON SKELETON OF SARPAGINE BY MASS SPECTROMETRY

K. Biemann
Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Mass.

(Received 25 May 1960)

SOME time ago several groups of investigators[2-4] simultaneously suggested structure I for sarpagine, isolated from Rauwolfia serpentina Benth. This alkaloid had been shown to possess a 5-hydroxy indole chromophore and the functional groups present in formula I. The alicyclic carbon skeleton, however, was arrived at largely by biogenetic considerations. Its rigorous proof by direct chemical intercorrelation of sarpagine with another indole alkaloid of established constitution, e. g., ajmaline, [5,6] though promised in one of the papers[3], was not presented.

---

[1] K. Biemann, C. Lioret, J. Asselineau, E. Lederer and J. Polonsky, Biochem. et Biophys. Acta in press.

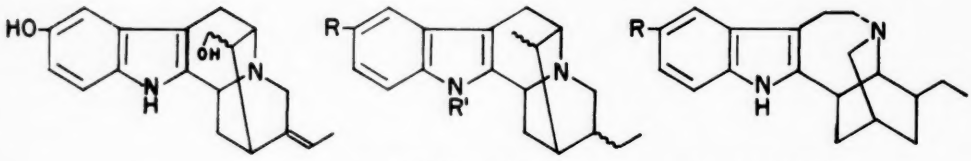
[2] D. Stauffacher, A. Hofmann and E. Seebeck, Helv. Chim. Acta 40, 508 (1957)

[3] W. Arnold, W. von Philipsborn, H. Schmid and P. Karrer, Helv. Chim. Acta 40, 705 (1957).

[4] J. Poisson, J. Le Men and M.-M. Janot, Bull. Soc. Chim. France 1957, 610.

[5] R. B. Woodward, Angew. Chem. 68, 13 (1956).

[6] R. Robinson, Angew. Chem. 69, 40 (1957).



I

II R = CH_3O R' = H
III R = H R' = CH_3

IV R = CH_3O
V R = H

It seemed to us that the correctness of the proposed structure could be checked by the comparison of the mass spectra of compound II (from sarpagine) and III (from ajmaline)[7], employing a minimum of chemical conversions and very little material.

These two compounds differ in the substitution of the indole nucleus but have an identical alicyclic carbon skeleton, apart from possible differences in the relative stereochemistry at two carbon atoms. Fragmentation on electron impact in a mass spectrometer of an aromatic molecule bearing an aliphatic or alicyclic substituent, in general, leaves the aromatic segment intact, which also retains the positive charge, whereas certain bonds in the nonaromatic part are preferentially broken. We would, therefore, expect structures II and III to have very similar spectra, in particular at the region of higher masses, which consists of the peaks due to the loss of fragments from the alicyclic moiety of the molecule. These peaks should be found at mass numbers sixteen units higher in the spectrum of II compared with III, since the net mass difference of the aromatic entities is due to one oxygen atom.

---

[7] R. B. Woodward and K. Schenker, unpublished.

1960

Sarpagine was converted *via* phenol-O-methylation[4], tosylation and reduction with lithium aluminium hydride to desoxy-methylsarpagine[3], m.p. 248-250°, mol. wt. 308 (by mass spectrometry). Two milligrams of it were hydrogenated in ethanol using platinum as a catalyst. After 20 min. the product, II, was isolated and sublimed at 0.1 mm. and 200° (bath); m.p. 237-240°. The mol. wt. of 310, exhibited by the mass spectrum, indicated the formation of a dihydro derivative, eliminating the necessity for elemental analysis.

The partial mass spectra of II and III, shown in Figure 1, clearly exhibit a very close similarity and the shift of 16 mass units, demonstrating the identity of their alicyclic carbon skeletons and confirming structure I for sarpagine. The main difference is the peaks at m/e 279 (M-31) and m/e 280 (M-30) in the spectrum of II which, however, are due to the loss of the methoxy group, either as such (mass 31) or, with rearrangement of one hydrogen atom, as formaldehyde (mass 30). It is of interest to note that there are no characteristic peaks below mass 198 in II and 182 in III, respectively. These latter peaks are considered to be due to the β-carboline skeleton, after loss of ring D and the one carbon bridge, followed by aromatization.

To exemplify the validity of the tacit assumption that indole alkaloids with different alicyclic carbon skeletons in fact give rise to quite dissimilar mass spectra, the spectra of ibogaine (IV)[8] and ibogamine (V)[8] are shown in Figure 1. Here again the high mass parts are very similar (in ibogaine 30 mass units higher, because of the additional methoxyl group), but definitely different from the spectra of II and III. There is, however,

---

[8] M. F. Bartlett, D. F. Dickel and W. I. Taylor, J. Amer. Chem. Soc. 80, 126 (1958).

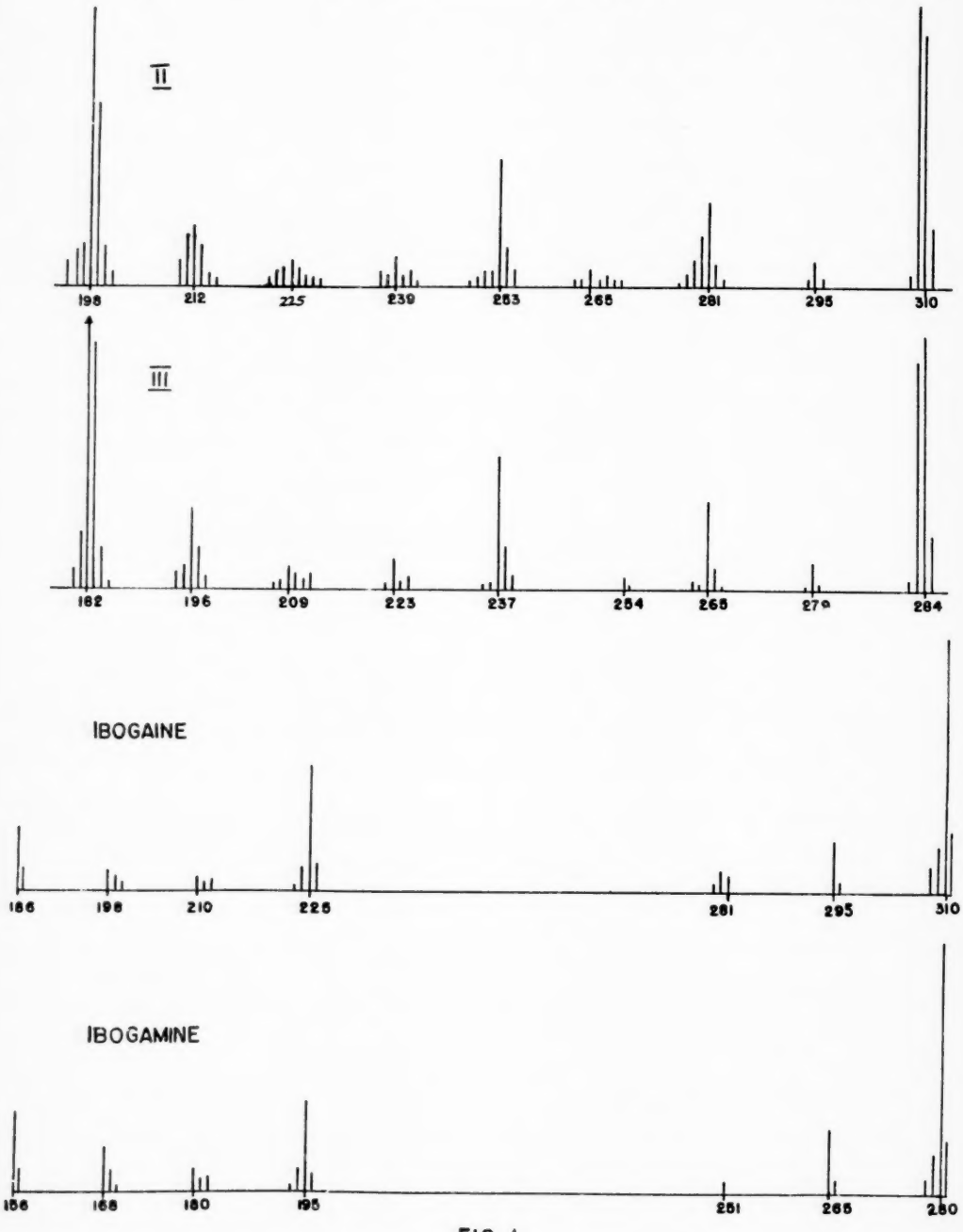

II
198
212
225
239
253
268
281
295
310
III
182
196
209
223
237
254
268
279
284
IBOGAINE
186
198
210
225
281
295
310
IBOGAMINE
166
168
180
195
251
265
280

FIG. 1.

1960

clearly present a group of peaks (at m/e 122, 123, 124, 135, 136, 148, 149, 154, not shown in Figure 1 for lack of space) which are identical in the spectra of both ibogamine and ibogaine, and therefore arise from the alicyclic parts. This points out that the molecular ion formed originally can also decompose into highly stabilized fragments not containing the indole grouping, probably because the seven-membered ring C prevents decomposition to a β-carboline. This behavior on electron impact is somewhat paralleled by the fact that the alkaloids of the ibogaine family, in contrast to sarpagine, yield 3-ethyl-5-methylpyridine under various pyrolyti conditions.[9,10]

We feel that this investigation points out some of the potentialities mass spectrometry has in this field. It might well become very useful for the relatively facile and speedy comparison of aliphatic or alicyclic carbo skeletons attached to similar aromatic nuclei in these more complicated cases where the structure of this part of the molecule cannot be deduced by direct interpretation of the spectrum of the unknown compound itself. The relative insensitivity of mass spectra to differences in the stereochemistr of certain groups, which lead only to differences in the intensity but not in the mass numbers of the peaks, is an added advantage in this case.

---

[9] R. Goutarel, M.-M. Janot, F. Mathys and V. Prelog, Compt. rend. 237, 1718 (1953).

[10] R. Goutarel, F. Percheron, J. Wohlfahrt and M.-M. Janot, Ann. pharm. franc. 15, 353 (1957).

Furthermore, it should be noted that all the spectra discussed above have been obtained with samples ranging from 30-100 micrograms.*

A more detailed discussion of the spectra and deuteration experiments, which further corroborate the position of the alcoholic hydroxyl and of the double bond, will be published elsewhere.

Acknowledgments - The author is greatly indebted to Prof. R. B. Woodward for a sample of compound III, to Dr. A. Hofmann for sarpagine, to Dr. W. I. Taylor for ibogaine and ibogamine, and to the National Science Foundation for financial support (Grant G5051).

---

* The spectra were determined with a CEC 21-103C mass spectrometer, equipped with heated inlet system, operated at 140°.

Tetrahedron Letters No.15, pp. 15-17, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

CONCERNING RING A OF CUCURBITACIN B

C.R. Noller, A. Melera and M. Gut

Department of Chemistry and Chemical Engineering

Stanford University, Stanford, California

J.N. Shoolery and L.F. Johnson

Varian Associates, Palo Alto, California

(Received 2 June 1960)

THE nuclear magnetic resonance (NMR) spectra of compounds having an α,β-unsaturated ketone group with hydrogen on the β carbon atom show signals from 13 to 54 c.p.s. downfield from benzene at 40 Mc.,[1] which corresponds to the region between $\delta = 6.76$ and $\delta = 7.77$ as defined here.[2] The NMR spectra of diosphenols prepared by the air oxidation of an alkaline solution of dihydro- and dihydrodeacetoxycucurbitacin B,[3]

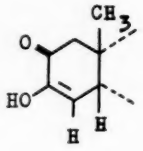
---

[1] J.N. Shoolery and Max T. Rogers, J. Am. Chem. Soc. 80, 5126 (1958).

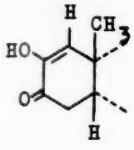
[2] All values reported here are at 60 Mc./sec. referred to tetramethylsilane in deuterochloroform solution. Chemical shifts are reported in parts per million according to the definition $\delta_i = 10^6(\nu_i - \nu_{ref.})/\nu_{ref.}$, which results in positive values of δ downfield from tetramethylsilane.

[3] A. Melera and C.R. Noller, manuscript submitted to J. Org. Chem. May 9, 1960.

which have hydroxyl on the α carbon atom of the α,β-unsaturated carbonyl grouping, lacked this peak and threw doubt on the presence of the diosphenol structure. Accordingly the two diosphenols having the partial structures I and II, and known respectively as forms A and B of 2,3-cholestanedione,[4] were prepared and their NMR spectra



I



II

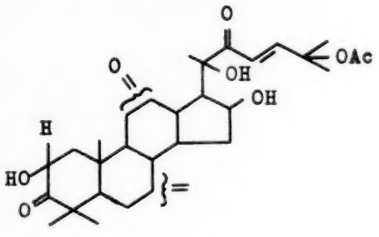
determined. Neither compound gave a signal between $\delta = 6.76$ and $\delta = 7.77$. However, form B showed a single sharp peak at $\delta = 6.37$, indicating that the effect of the α hydroxyl group is to shift the signal arising from the β hydrogen to higher field strength. In form A this singlet is split into a sharp doublet centered at $\delta = 5.68$, which may be ascribed to the spin-spin interaction of the β proton with the proton on C-5, this proton being lacking in form B. The coupling constant is about 3 c.p.s. The diosphenols prepared from cucurbitacin B also show this doublet centered at $\delta = 5.97$. Hence, they also must have one hydrogen β and one

---

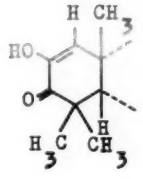
[4] E.T. Stiller and O. Rosenheim, J. Chem. Soc. 353 (1938); L. Ruzicka, P.A. Plattner, and M. Furrer, Helv. Chim. Acta 27, 524 (1944).

hydrogen γ to the carbonyl group.

On the basis of the various structures (III) recently proposed for cucurbitacin B,[5] the diosphenols should have partial structure IV,



III



IV

but IV does not have the grouping required by the NMR spectra. Neither can the proper grouping be placed in any other position of the proposed carbon skeleton. If the structure of ring A is essentially correct as shown in III, the NMR spectra can be accommodated only if there is no angular methyl group at C-10.

Acknowledgment. The chemical portion of this work was supported in part by a research grant, RG-5076, from the National Institutes of Health, U.S. Public Health Service.

---

[5] D. Willner, P.R. Enslin, J.M. Hugo, and K.B. Norton, Chem. and Ind. (London) 951 (1959); D. Lavie and Y. Shvo, ibid. 403 (1960).

Tetrahedron Letters No.15, pp. 18-22, 1960. Pergamon Press Ltd.
Printed in Great Britain

GIBBERELLIN A_7. A NEW FUNGAL GIBBERELLIN

B.E. Cross, R.H.R. Galt and J.R. Hanson

Imperial Chemical Industries Limited,
Akers Research Laboratories, Welwyn, Herts.

(Received 3 June 1960)

THE fungus Gibberella fujikuroi has been shown[1] to produce four gibberellins, namely, gibberellins A_1, A_2 and A_4 and gibberellic acid, whilst gibberellins A_1 and A_5 have been isolated from the immature seed of Phaseolus multiflorus.[1] We wish to report the isolation of another gibberellin from Gibberella fujikuroi. The fungus was cultured[2] until the inorganic nitrogen was exhausted from the medium, then the pH was adjusted to and maintained at 7 for 209 hours. Isolation of crude gibberellic acid as previously described[2,3] and recovery of the ethyl acetate mother liquors afforded a gum which was adsorbed on a column of charcoal-celite (1:2) and eluted with increasing concentrations of acetone in water. The fraction eluted with water containing 65% acetone gave a gum which was chromatographed on silica-celite (1:2) and eluted with increasing concentrations of ethyl acetate

---

[1] For review see P.W. Brian, J.F. Grove and J. MacMillan, "The Gibberellins", in Zechmeister, Prog. Chem. Org. Nat. Prod. 18, 350 (1960).

[2] Brit. Pat. 783611.

[3] P.J. Curtis and B.E. Cross, Chem. and Ind. 1066 (1954).

1960

in chloroform. The fraction obtained with 20% ethyl acetate gave a new plant growth promoting acid (25 mg./l. of culture filtrate) for which we propose the name gibberellin A_7.

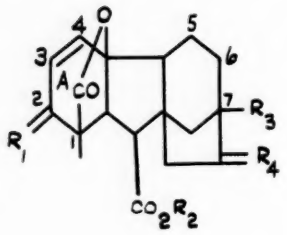
Analysis of gibberellin A_7 (I), m.p. 202° dec., $[\alpha]_D^{24}$ +20° (EtOH), ν_{max} 3450 (OH), 1742, 1722 (C=O), 1654 cm.$^{-1}$ (C=C), $\nu_{max}^{CH_3CN}$ 1772 (γ-lactone), 1738 (CO_2H), 1657 cm.$^{-1}$ (C=C), and its methyl ester (II), m.p. 152-153° or 168-170°, $[\alpha]_D^{23}$ +33° (EtOH), $\nu_{max}^{CHBr_3}$ 3574, 1766, 1722, 1655, 886 ($=CH_2$), 780, 760 and 743 cm.$^{-1}$ ($^{H}\!\!\searrow\!C = C\!\!\swarrow^{H}$) indicates the molecular formula $C_{19}H_{22}O_5$ for (I). Microhydrogenation revealed the presence of two double bonds; with concentrated sulphuric acid (I) gave an intense red colour (cf. gibberellic acid[4]).

Treatment of (I) with dilute mineral acid at 20° gave an aromatic acid $C_{18}H_{22}O_3$ (VI), m.p. 220-222°, ν_{max} 3415, 2634, 1678 and 1587 cm.$^{-1}$, λ_{max}^{EtOH} 269, ~272 mμ (ε 418, 377), which with diazomethane gave an ester $C_{19}H_{24}O_3$ (VII), m.p. 145-148°. Under similar conditions gibberellic acid (III) gives allogibberic acid[5] (VIII), suggesting that (I) has the same ring A structure as gibberellic acid, whilst the addition of water to the terminal methylene group is analogous to the

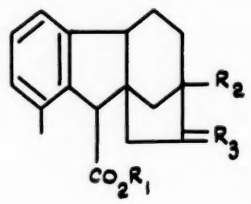
---

[4] B.E. Cross, J. Chem. Soc. 4670 (1954).

[5] P.W. Brian, J.F. Grove, H.G. Hemming, T.P.C. Mulholland and M. Radley, Plant Physiol. 329 (1958).



	R_1	R_2	R_3	R_4
I	H, OH	H	H	CH_2
II	H, OH	Me	H	CH_2
III	H, OH	H	OH	CH_2
IV	O	Me	H	CH_2
V	H, OH	Me	H	O

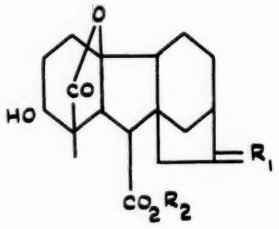


	R_1	R_2	R_3
VI	H	H	OH, Me
VII	Me	H	OH, Me
VIII	H	OH	CH_2

IX R_1 = CH_2 R_2 = H

X R_1 = OH, Me R_2 = H

XI R_1 = H, Me R_2 = Me



1960

conversion[1,8] of gibberellin A_4[1,6] (IX) to gibberellin A_2[1,7] (X).

Hydrogenation of (II) over 25% palladised charcoal gave 60% of acidic products and dihydrogibberellin A_4 methyl ester[7] (XI), m.p. 148-151°, identified by mixed m.p. and infrared spectrum. The Δ^3 position of the double bond, suggested by acid rearrangement, was confirmed by the high yield of hydrogenolysis acids (cf. gibberellic acid[9]) and by the oxidation of (II) with manganese dioxide to an $\alpha\beta$-unsatured ketone $C_{20}H_{22}O_5$ (IV), m.p. 139-140°, λ_{max}^{EtOH} 228 mμ (ε 6900), $\nu_{max}^{CHCl_3}$ 1776 (γ-lactone), 1724 (ester) and 1691 cm.$^{-1}$ ($\alpha\beta$-unsaturated ketone).

Oxidation of (I) with sodium periodate/potassium permanganate followed by spectrophotometric determination[10] of the formaldehyde showed the presence of a terminal methylene group. Ozonolysis of (II) with 1 mole of ozone yielded formaldehyde (0.43 mol.) and a nor-ketone $C_{19}H_{22}O_6$ (V), m.p. 185°, ν_{max} 3440, 1784, 1755 (5-ring ketone), 1738 cm.$^{-1}$, which although it gave a monoacetate, m.p. 187-189°, was stable to periodate and therefore not an α-ketol.

On the basis of structure (IX) for gibberellin A_4, the only

---

[6] N. Takahashi, Y. Seta, H. Kitamura and Y. Sumiki, Bull. Agric. Chem. Soc. Japan, 21, 396 (1957).

[7] Idem, ibid. 23, 405 (1959).

[8] J.F. Grove, personal communication.

[9] B.E. Cross, J. Chem. Soc. 1960, in the press.

[10] R.U. Lemieux and E. von Rudloff, Canad. J. Chem. 33, 1710 (1955).

structure for gibberellin A_7 consistent with these results is (I), i.e. 7-deoxygibberellic acid.

All structures are supported by satisfactory analyses; infrared frequencies refer to 'Nujol' mulls unless otherwise stated.

We are indebted to Mr. E.G. Jefferys and his colleagues for carrying out the fermentations.

Tetrahedron Letters No.15, pp. 23-30, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

THE CONFIGURATION OF DELPHININE

K. Wiesner, D. L. Simmons and R. H. Wightman

Organic Chemistry Laboratory, University of New Brunswick
Fredericton, Canada

(Received 3 June 1960)

THE complete structure of delphinine (XIV)[1] and aconitine (I)[2] have been proposed with a remaining ambiguity in the location of the ring A substituents. This ambiguity was subsequently removed[3] and the two compounds directly correlated[4].

Independently, the structure, relative and absolute configuration of desmethanol aconinone was determined by X-ray crystallography[5,6].

---

[1] K. Wiesner, F. Bickelhaupt, D. R. Babin and M. Gőtz, Tetrahedron Letters 3, 12 (1959).

[2] K. Wiesner, M. Gőtz, D. L. Simmons, L. R. Fowler, F. W. Bachelor, R. F. C. Brown and G. Büchi, Tetrahedron Letters 2, 15 (1959).

[3] F. W. Bachelor, R.F.C. Brown and G. Büchi, Tetrahedron Letters 10, 1 (1960).

[4] K. Wiesner, D. L. Simmons and L. R. Fowler, Tetrahedron Letters 18, 1 (1959).

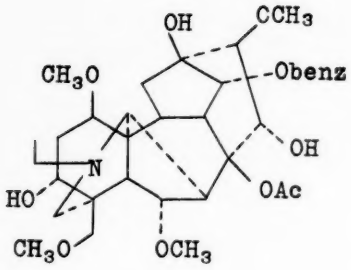
[5] M. Przybylska and L. Marion, Can. J. Chem. 37, 1116 (1959).

[6] M. Przybylska and L. Marion, Can. J. Chem. 37, 1843 (1959).

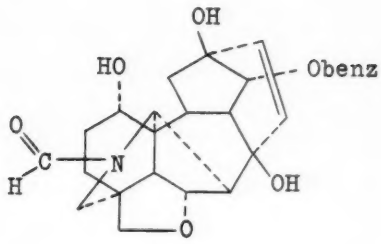
The X-ray work[5,6] settled the configuration of all asymmetric centres in aconitine except the configuration of the ring A substituents. The configuration of the C_3 hydroxyl was rigorously proved by Büchi[3] and the configuration of the C_1 methoxyl suggested by the same author on the basis of an ingenious conformational argument[3]. Thus, it is possible[3] to write the complete expression I for aconitine.

We have now proved rigorously that the configuration of the C_1 methoxyl in delphinine is trans to the nitrogen bridge. Since in the correlation[4] of aconitine and delphinine, the C_1 and C_6 substituents remain undisturbed, our result constitutes a corroboration of Büchi's conformational argument.

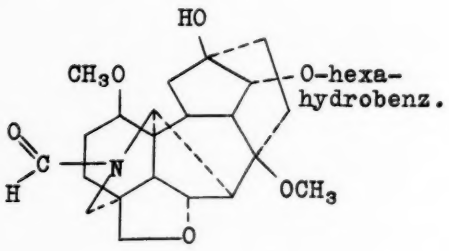
Our starting materials were the two demethylation products II and III[1]. We have proved that in II the C_1 hydroxyl is cis to the nitrogen bridge and that the demethylation of the C_1 methoxyl proceeds with inversion of configuration. Compound II was hydrogenated with platinum oxide in glacial acetic acid to the octahydroderivative IV (m.p. 241°). Found: C, 63.76; H, 7.62; OCH_3, 0.0. Calc. for $C_{27}H_{37}O_7N.H_2O$: C, 64.14; H, 7.78%. Compound IV was saponified for three hours with 3% aqueous ethanolic barium hydroxide. The product was a mixture of compounds V and VI.



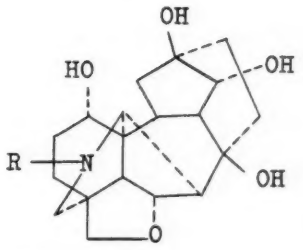
(I)



(II)

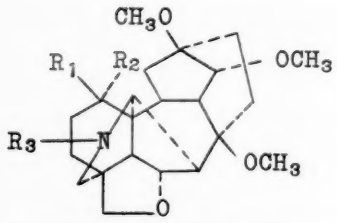


(III)



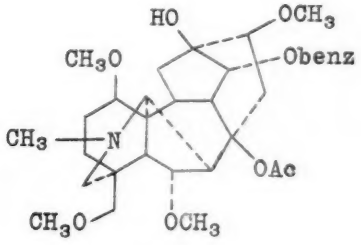
(V) R = H

(VI) R = -C(=O)H

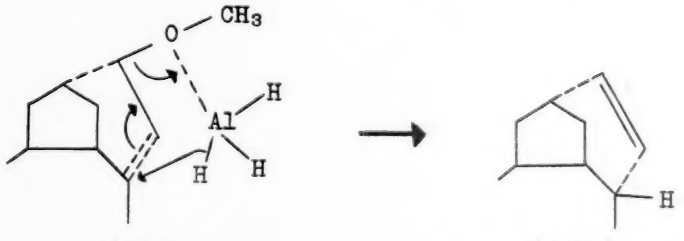


(IX) R_2=OCH_3, R_1=H

(X) R_2=H, R_1=OCH_3



(XIV)



(XII)

(XIII)

V (m.p. 265°C) Found: C, 63.19; H, 7.75. Calc. for $C_{19}H_{27}O_5N \cdot \frac{1}{2}H_2O$: C, 63.65; H, 7.87%. I.R.: no formamide band.

VI (m.p. 164°) Found: C, 61.15; H, 7.51. Calc. for $C_{20}H_{27}O_6N.H_2O$: C, 60.75; H, 7.39%. I.R. (KBr): 1645 cm^{-1} (formamide).

The easy hydrolysis of the formamide group may be explained by the participation of the C_1 hydroxyl in this process.

The oxidation of II with chromium trioxide gave the corresponding C_1 ketone VII[7]. Treatment of this compound with sodium borohydride resulted in the reduction of the C_1 keto group and saponification of the benzoyl group. The product VIII thus obtained (m.p. 310°, Found: C, 64.25; H, 6.79. Calc. for $C_{20}H_{25}O_6N$: C, 63.96; H, 6.72. I.R.: 1650 cm^{-1} (formamide)) was found to be identical with the product of a very mild direct saponification of II. This proves conclusively the configuration of the C_1 hydroxyl in II since the formation of a equatorial C_1 alcohol is favoured both by thermodynamic and by kinetic factors in the reduction of a C_1 ketone.

Compound VI was methylated first with methyliodide and

---

[7] W. A. Jacobs and S. W. Pelletier, J. Am. Chem. Soc. 76, 161 (1954).

1960

silver oxide in dimethyl formamide[8] and the amorphous product of this reaction was methylated again with diazomethane-borontrifluoride in methylene chloride[9]. The product of the second methylation, after purification by chromatography on alumina, was a glass which showed in the infrared spectrum no hydroxyl peak and a formamide peak at 1672 cm^{-1}. Clearly, this material had the structure IX ($R_3 = -C\lesssim^{O}_{H}$). It was reduced by lithium aluminum hydride, and the resulting basic product was purified by chromatography on alumina. Benzene-ether (9:1) eluted the crystalline base IX ($R_3 = -CH_3$). It melted after several crystallizations from petroleum ether at 156° and was sublimed in high vacuo for analysis. Found: C, 68.81; H, 8.94; OCH_3, 29.88. Calc. for $C_{24}H_{37}O_5N$: C, 68.79; H, 8.90; 4-OCH_3, 29.63%.

The hexahydrobenzoyl ester III was saponified to the corresponding alcohol XI (m.p. 256°). Found: C, 63.40; H, 7.57; OCH_3, 15.23. Calc. for $C_{22}H_{31}O_6N \cdot \frac{1}{2}H_2O$: C, 63.75; H, 7.78; OCH_3, 14.98%.

Compound XI was now subjected to the same methylation procedure which was applied previously to compound VI. The product X ($R_3 = -C\lesssim^{O}_{H}$) was crystalline and was recrystal-

---

[8] J. Goerdeler and J. Galinke, Chem. Ber. 90, 203 (1957).

[9] E. Müller and W. Rundel, Angew. Chemie p. 105 (1958).

lized from methanol to a melting point of 203°. Found: C, 66.48, 66.76; H, 8.10, 8.27; OCH_3, 28.75. Calc. for $C_{24}H_{35}O_6N$: C, 66.57; H, 8.17; 4-OCH_3, 28.67. I.R. (CCl_4): no OH band, 1668 cm^{-1} (formamide).

The above compound was reduced by lithium aluminum hydride to the basic compound X ($R_3 = -CH_3$). This product crystallized after chromatography on alumina (eluent, benzene-ether 9:1) and was recrystallized from methanol to a melting point of 185°. Found: C, 68.53, 68.86; H, 8.62, 8.98; OCH_3, 29.56, 29.95. Calc. for $C_{24}H_{37}O_5N$: C, 68.79; H, 8.90; 4-OCH_3, 29.63%.

Both compounds IX and X ($R_3 = -CH_3$) are clearly epimeric at C_1. Since IX has been shown to have an equatorial C_1 methoxyl, compound X, which contains the undisturbed original C_1 methoxyl of delphinine, must have this substituent in the axial configuration portrayed in the formula X. The fact that IX and X ($R_3 = -CH_3$) differ in nothing but the configuration of one asymmetric centre is supported by the great similarity of their infrared spectra (which, however, clearly show nonidentity) and by the practical identity of their N.M.R. spectra.

It has been already proposed by Büchi[3] that all remaining substituents of delphinine have the same configuration as the corresponding substituents of aconitine. This is, of course, biogenetically very plausible, but it is rigorously

1960

proved only for the C_1 and C_6 methoxyls which remained unaffected in the correlation[4]. Of the remaining substituents of delphinine, only the configuration of the C_{14} methoxyl and C_{19} benzoxy group could be different in delphinine and aconitine. There are some tentative chemical arguments which suggest that these substituents have, in fact, the identical configuration in delphinine and aconitine. The stability of compound II under conditions where all methoxyls have undergone an acid catalyzed cleavage suggests that the benzoxy group may have a configuration syn to the double bond. If the configuration were anti to the double bond, one might expect a great reactivity of the corresponding homoallylic system[10].

If the pyro-isopyro rearrangement (which is an extremely unusual bridgehead allylic rearrangement[11]) is a concerted process which does not involve the mesomeric allylic cation as intermediate, it would be favoured by a cis relationship of the C_{14} and C_8 substituents; especially the allylic rearrangement of pyro derivatives[12] on lithium aluminum hydride reduction may be conveniently formulated as XII $\longrightarrow$ XIII.

---

[10] S. Winstein, M. Shatavsky, C. Norton and R. B. Woodward, J. Am. Chem. Soc. 77, 4183 (1955).

[11] K. Wiesner, F. Bickelhaupt and D. R. Babin, Experientia 15, 33 (1959).

[12] K. Wiesner, H.W. Brewer, D.L. Simmons, D.R. Babin, F. Bickelhaupt, J. Kallos and T. Bogri, Tetrahedron Letters 3, 17 (1960).

Thus, it seems to be very probable that the formula XIV is a correct expression for both the absolute and relative configuration of delphinine.

Tetrahedron Letters No.15, pp. 31-39, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

A CONTRIBUTION TO THE SKELETAL STRUCTURE OF RYANODINE

D.R. Babin, J.A. Findlay, T.P. Forrest, F. Fried, M. Götz, Z. Valenta and K. Wiesner

Organic Chemistry Laboratory, University of New Brunswick Fredericton, Canada

(Received 7 June 1960)

SOME time ago we have reported[1] the hydrolysis of the insecticide ryanodine, $C_{25}H_{35}O_9N$, to pyrrole-α-carboxylic acid and ryanodol, $C_{20}H_{32}O_8$. On treatment with 10% aqueous sulphuric acid overnight, ryanodol eliminates a molecule of water and yields anhydroryanodol[2] which has now been obtained crystalline and recrystallized from acetone-ether (m.p. 244°). Found: C, 62.76; H, 8.06; O, 29.35. Calc. for $C_{20}H_{30}O_7$: C, 62.82; H, 7.91; O, 29.29%. I.R. (KBr): 1723 cm^{-1} (broad).

Anhydroryanodol consumes one mole of periodic acid and yields oxoanhydroryanodol which crystallizes readily from acetone (m.p. 259°). Found: C, 62.92; H, 7.26; O, 29.60. Calc. for $C_{20}H_{28}O_7$: C, 63.14; H, 7.42; O, 29.43%.

---

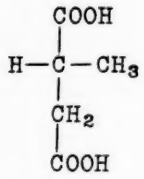
[1] R. B. Kelly, D.J. Whittingham and K. Wiesner, Can. J. Chem. 29, 905 (1951).

[2] R.B. Kelly, D.J. Whittingham and K. Wiesner, Chem. and Ind., p. 857 (1952).

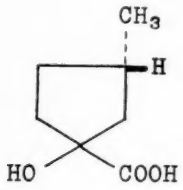
Ryanodol itself consumes two moles of periodic acid in acidic solution and yields oxoryanodol, m.p. 207°, which may be recrystallized from acetone. Found: C, 58.21; H, 7.14; O, 34.73; C-CH_3, 11.61. Calc. for $C_{20}H_{28}O_8 \cdot H_2O$: C, 58.10; H, 7.30; O, 34.75; 4 C-CH_3, 14.17%. I.R.: 1778 cm^{-1} (γ-lactone), 1718 cm^{-1}. The N.M.R. spectrum showed absence of vinylic hydrogens and of aldehyde groups. A singlet at 1.93 ppm. with an area 1H was assigned to a formate ester group. Such a group must be formed by periodate cleavage of a hemiacetal. Mild alkaline hydrolysis of oxoryanodol gave 0.65 moles of isobutyric acid and formic acid, both identified by partition chromatography on silicic acid. The isobutyric acid was further converted into the crystalline amide, m.p. 128°, which was identical by mixed melting point and infrared spectrum with an authentic specimen.

In phosphate buffer (pH=6.8), ryanodol consumes three moles of periodate in two hours. The product was extracted by ether and chromatographed on silicic acid. The first chloroform fractions contained a compound which crystallized from acetone, m.p. 192°. Found: C, 60.99; H, 6.66; O, 32.10. Calc. for $C_{20}H_{26}O_8$: C, 60.96; H, 6.65; O, 32.49%. I.R. (KBr): 1770 (γ-lactone), 1740, 1696 cm^{-1}. The infrared spectrum in CCl_4 indicated the absence of hydroxy groups. The N.M.R. spectrum showed absence of

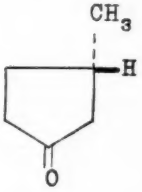
1960



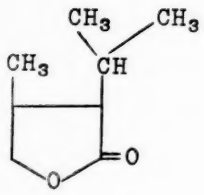
(I)



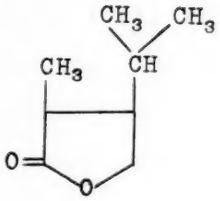
(II)



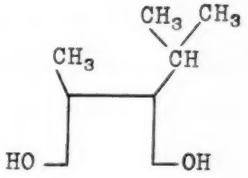
(III)



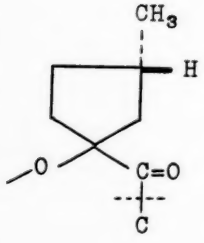
(IVa)



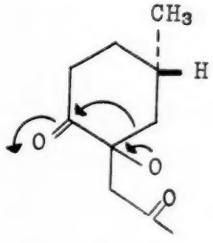
(IVb)



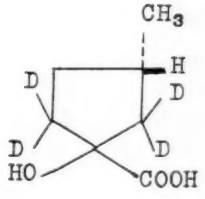
(V)



(VI)



(VII)



(VIII)

vinylic hydrogens and aldehydes and a singlet with an area 1H at 1.93 ppm. ascribed to a formate ester. The N.M.R. spectrum further showed five C-methyls with a total area of 15H at 8.60, 8.91, 8.94, 9.03 and 9.19 ppm. This is in agreement with many Kuhn-Roth determinations on various ryanodol derivatives which indicate the presence of three to four C-methyls, and with the known presence of a geminal dimethyl group.

From the results of the periodate cleavages it appears probable that ryanodol has at least six hydroxyls. This would mean that the skeleton contains three carbon rings and two cyclic ethers. We have already reported[2] that an alkaline hydrolysis of anhydrooxoryanodol yields almost a full mole of isobutyric acid. We have now repeated the hydrolysis of oxoanhydroryanodol by 5% ethanolic potassium hydroxide under reflux for 6 hours on a large scale. The acidic products of this reaction were extracted, hydrogenated with platinum oxide in acetic acid and separated by partition chromatography on silicic acid into three fractions eluted by (a) chloroform, (b) 5% butanol in chloroform, and (c) 20% butanol in chloroform.

The fraction (c) was crystalline and after crystallization from chloroform melted at 108–110°. Found: C, 45.49; H, 6.08; O, 48.44; C-CH_3, 6.82; neutralization equivalent, 66.0. Calc. for $C_5H_8O_4$: C, 45.46; H, 6.10;

1960

O, 48.44; 1 C-CH_3, 11.35; neutralization equivalent, 66.05. The compound was found to be identical by mixed melting point and infrared spectrum with authentic methylsuccinic acid (I). The best yield in several runs was 0.54 moles, the average yield was about 0.5 moles.

Fraction (b) crystallized from benzene and melted at 90-91° after sublimation in vacuo. Found: C, 58.41; H, 8.34; C-CH_3, 6.13; neutralization equivalent, 137. Calc. for $C_7H_{12}O_3$: C, 58.38; H, 8.40; 1 C-CH_3, 10.4; neutralization equivalent, 144. Treatment of the acid with diazomethane gave an oily ester which showed in the infrared a hydroxyl peak and an ester peak at 1725 cm^{-1}. The acid may be assigned the structure II. Lithium aluminum hydride reduction of the methyl ester gave an oily diol which took up one mole of periodic acid and yielded the methylcyclopentanone III characterized as a 2,4-dinitrophenylhydrazone, m.p. 134.5°. Found: C, 51.91; H, 5.15; N, 19.62; O, 23.34. Calc. for $C_{12}H_{14}N_4O_4$: C, 51.84; H, 5.08; N, 20.16; O, 23.02%. The infrared spectrum of this derivative was superimposable with the spectrum of an authentic sample of racemic 3-methylcyclopentanone-2,4-dinitrophenylhydrazone. The rotation dispersion curve of the natural ketone III showed a negative Cotton effect.

This requires[3] that this compound be assigned the absolute configuration shown in formula III.

The best yield of compound II was 0.46 moles.

Fraction (a) of the silicic acid chromatogram was rechromatographed on alumina. Petroleum ether-benzene (1:1) eluted a liquid γ-lactone which was distilled at 80° in vacuo (outside temp., 1 mm). Found: C, 67.21; H, 9.75; O, 23.41; M.W. (mass spectroscopy)[4], 142. Calc. for $C_8H_{14}O_2$: C, 67.57; H, 9.93; O, 22.51; M.W., 142. The infrared spectrum showed a γ-lactone band at 1785 cm^{-1}. The N.M.R. spectrum indicated the presence of three C-methyl groups.

Since we had already identified isobutyric acid as one of the fragments we assumed that the lactone might have the structure IVa or IVb. The lactone was reduced with lithium aluminum hydride to the oily diol V. The structure V for the diol was rigorously proved as follows. One isomer (m.p. 175°) of methylisopropylsuccinic acid[5] was

---

[3] c.f. Carl Djerassi: Optical Rotatory Dispersion, McGraw-Hill Book Co. Inc., New York (1960), p. 103.

[4] We wish to thank Dr. Klaus Biemann, Chemistry Dept., M.I.T., Cambridge, Mass., for the determination of the mass spectrum. Dr. Biemann also suggested on the basis of the mass spectrum a methyl isopropyl structure for this compound.

[5] C. S. Marvel and J. A. Fuller, J. Am. Chem. Soc. 74, 1506 (1952).

1960

esterified with diazomethane and the ester reduced with lithium aluminum hydride. The resulting oily diol was shown to be identical by infrared and N.M.R. spectra with the 'natural' reduction product V. An examination of the hydrolysis mixture of anhydrooxoryanodol prior to hydrogenation revealed the presence of compounds I and II in an undiminished yield.

We next turned our attention to the problem of the genesis of compound II. In principle, there were two possibilities for its formation. These are portrayed in the structures VI and VII. The possibility VI clearly means that the skeleton of compound II is present in anhydrooxoryanodol, the possibility VII envisages the formation of the acid II by a base catalyzed rearrangement of an actual or potential methylcyclohexane dione. We performed the hydrolysis of anhydrooxoryanodol in a deuterated medium (EtOD + D_2O + KOD) and isolated the deuterated compound VIII in which the deuterium atoms are not exchangeable. Compounds VIII and II had identical melting points and did not show any melting point depression on admixture. The infrared spectra of both compounds were very similar. The N.M.R. spectra of the esters of II and VIII showed identical peaks at 6.32 ppm (3H) methoxyl, 7.24 ppm (1H) hydroxyl, 8.98, 9.06 ppm (3H) C-CH_3. The only difference in the two spectra was the multiplet between 7 and 8.78 ppm which had

an area of 7H in II and an area of 3H in VIII. A determination of deuterium in VIII gave 29.1 atom % XSSD (Calc. for $C_7H_8D_4O_3$ 33 atom % XSSD). This clearly shows that acid II is formed from a six-membered ring precursor present in anhydrooxoryanodol.

Deuterated methylsuccinic acid I was also isolated. It has a deuterium content of 31.58 atom % XSSD and the N.M.R. spectrum of the dimethyl ester showed that the C-methyl group was completely unlabeled. The methyl group was furthermore split into a triplet due to deuterium in the α position. This finding proves rigorously that the methyl group of (I) had been originally present in ryanodol and not created in the basic hydrolysis. The yields of I and II in five runs were almost precisely complementary to one mole. Since, however, a theoretical yield is exceedingly improbable, it seems that the two fragments are not formed from the same carbons. In any case, it is not possible to visualize a mode of formation of I and II in which these two compounds would have more than one single carbon in common. Formally, IV and I could originate from the same carbon atoms. A precursor of the fragment IV could lose acetone and yield a precursor of the fragment I. However, this is exceedingly improbable as the sum of the yields of I and of isobutyric acid clearly exceeds one mole. It would be necessary to assume a second geminal dimethyl group

in ryanodol and this does not seem possible. Consequently, it appears that most of the carbon atoms of ryanodol have been characterized in the fragments I, II and IV.

It is clear that ryanodol is a diterpenoid of a quite unusual type. In order to incorporate the known skeletal elements into a plausible diterpenoid biogenesis, one has to perform a considerable number of rearrangements and/or ring openings, or one has to cyclize the diterpenoid chain in a quite unusual manner.

We wish to thank the Ciba Pharmaceutical Products Inc., Summit, New Jersey, and the Research Corporation, New York, for grants which enabled us to undertake this investigation. M.G. wishes to thank the National Research Council, Ottawa, for a postdoctoral fellowship.

The supply of plant material by S. B. Penick and Company, New York, is gratefully acknowledged.

Tetrahedron Letters No.16, pp. 1-3, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

REDUCTION OF ORGANIC COMPOUNDS BY LITHIUM IN LOW MOLECULAR WEIGHT AMINES. HIGHLY SELECTIVE LITHIUM-AMINE REDUCING SYSTEMS

Robert A. Benkeser, Ram K. Agnihotri and Merwyn L. Burrous

Department of Chemistry, Purdue University, Lafayette, Indiana

(Received 7 June 1960)

WE have shown[1] that lithium dissolved in certain low molecular weight amines is a unique and potent reagent for reducing aromatic compounds selectively to monoolefins.

We are hereby reporting that even a greater selectivity can be achieved in these reductions by carrying out the reactions in a mixture of solvents rather than in the pure amine. It will be noted from Table 1, that the addition of materials like dimethylamine, isopropylamine and morpholine to the usual solvents for these reductions (methylamine, ethylamine and ethylenediamine), increases quite markedly, in most instances, the percentage of the more thermodynamically stable 1-alkylcyclohexene. An equally important advantage to this new technique is that it enables one to carry out the reductions in a much less volatile solvent system than was heretofor possible.

The presence of at least small amounts of methylamine, ethylamine, or ethylenediamine seems essential. In the presence of pure morpholine or

---

[1] See R.A. Benkeser, J.J. Hazdra, R.F. Lambert and P.W. Ryan, J. Org. Chem. 24, 854 (1959) for reference to the previous papers in this series.

dimethylamine, the reductions shown in Table 1 do not occur at any appreciable rate. On the other hand, cumene is reduced quite selectively to 1-isopropylcyclohexene in a solvent mixture containing 93 per cent dimethylamine and only 7 per cent methylamine by volume (entry 6 in Table 1).

It should be noted that not all the additives we tested showed the effects illustrated in Table 1. While reductions did occur in the presence of diluents like trimethylamine, ethyl ether and t-octylamine, the isomer ratios were essentially unaffected.

TABLE 1

Reduction of Aromatic Hydrocarbons by Lithium in Various Amines

Hydrocarbon reduced	Solvent	Per cent olefin distribution[a]	
		1-Alkylcyclohexene	3+4-Alkylcyclohexene
Toluene	methylamine	59	41
Toluene	CH_3NH_2 - Me_2NH(90)[b]	82	18
Cumene	methylamine	46	54
Cumene	CH_3NH_2 - i- $PrNH_2$(50)	65	19
Cumene	CH_3NH_2 - morpholine (75)	88	12
Cumene	CH_3NH_2 - Me_2NH(93)	82	18
Cumene	ethylenediamine[c]	76	19
Cumene	NH_2 -$(CH_2)_2NH_2$-morpholine (67)	87	13
Cumene	ethylamine	66	34
Cumene	$EtNH_2$ - Me_2NH(52)	85	15
t-Butylbenzene	ethylenediamine	70	30
t-Butylbenzene	$H_2N(CH_2)_2NH_2$-morpholine(66)	86	14
t-Butylbenzene	$EtNH_2$ - Me_2NH(52)	86	14

[a] The olefin mixtures were analyzed by vapor phase chromatography.

[b] The values in parentheses indicate percentage by volume in which the diluents were present.

[c] L. Reggel, R.A. Friedel and I. Wender, J. Org. Chem. 22, 891 (1957).

We have undertaken a broad program designed to assess the types of additives which affect the selectivity of these reductions, as well as to determine the cause of this effect. The latter is particularly intriguing, since the ultimate explanation may be intimately connected with the classical problem of the constitution of the "blue solutions" resulting from the solubility of metals in ammonia or amines.

The authors are grateful to the National Science Foundation and the National Institutes of Health for fellowship grants which made this work possible.

1960

Tetrahedron Letters No.16 pp. 4-10, 1960. Pergamon Press Ltd. Printed in Great Britain.

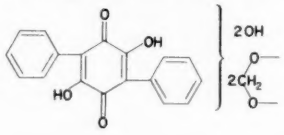
THE STRUCTURE OF THELEPHORIC ACID

K. Aghoramurthy, K. G. Sarma and T. R. Seshadri

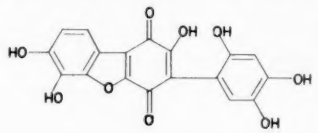
Department of Chemistry, University of Delhi

(Received 9 June 1960)

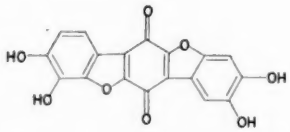
AFTER our first communication[1] on the structure of thelephoric acid (I) made last year, two papers have appeared on this subject, one proposing the formula (II) and/or a closely related isomer by Read and Vining[2], and the other advocating the formula (III) by Gripenberg[3] based mainly on spectroscopic



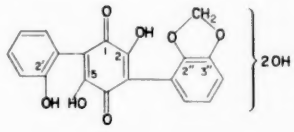
I



II



III



IV

evidences. We present below some more results of our experiments and our conclusions based on them which lead to a small revision of our original structure as in (IV).

(i) Heterogeneity of thelephoric acid samples:

Read and Vining[2] suggested that the thelephoric acid samples may be

---

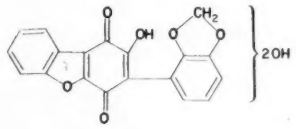
[1] K. Aghoramurthy, K.G. Sarma and T.R. Seshadri, Tetrahedron Letters No. 8, 20 (1959).

[2] G. Read and L.C. Vining, Canad. J. Chem. 37, 1442 (1959).

[3] J. Gripenberg, Suomen Kemistilehti, 33B, 72 (1960).

heterogeneous though they advanced no direct evidence. We have examined the I.R. and X-ray spectra of the following samples of thelephoric acid: (A) sample obtained by us from the lichen Lobaria isidiosa Wain.; (B) sample obtained by Asahina and Shibata from the lichen Lobaria retigera;[4] (C) sample of Gripenberg isolated from the fungus Hydnum aurantiacum Batsch[5] and (D) our sample after being heated at 200° in high vacuum for 7 hr.

The I.R. spectra of all natural samples (A, B & C) taken in potassium bromide agree in general though there are some minor differences, but the absorption peaks are not very well defined. In the case of (D), absorption peaks tend to become sharper and well defined and there are some definite differences as compared with others. Thus heating seems to produce a marked effect. This effect is also shown in the X-ray patterns. It could be reasonably concluded that the natural samples contain a predominantly major entity (formula IV) and a minor entity (formula V), and heating at 200° in vacuo produces more of the latter. This is also supported by analytical values given in Table 1.



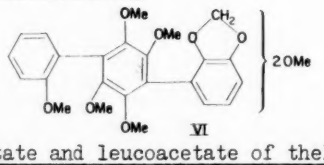
V

(ii) Leucothelephoric acid methyl ethers:

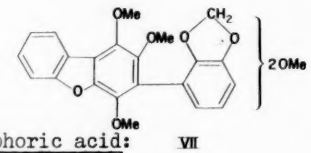
The formation of two methyl ethers (after catalytic hydrogenation followed by methylation with diazomethane) in Kögl et al.[6] as well as in our experiments[1] could now be explained on the above basis. The major product m.p. 254-256° obtained is the heptamethyl ether of leucothelephoric

4 Y. Asahina and S. Shibata, Ber. 72, 1531 (1939).
5 J. Gripenberg, Acta Chem. Scand. 12, 1411 (1958).
6 F. Kögl, H. Erxleben and L. Jänecke, Ann. 482, 105 (1930).

acid (VI) and the minor product may be its pentamethyl ether (VII) corresponding to the dehydrated form. The latter could not be studied by us because of paucity of material; it would appear that for the same reason Kögl et al.[6] also did not examine it in detail. We have now carried out the reduction and methylation of thelephoric acid in aqueous medium using alkaline sodium hydrosulphite and dimethyl sulphate and obtained only the heptamethyl ether (VI), m.p. 254-256° and none of the second product (VII). It seems to be possible that the minor entity might have undergone ring opening under the alkaline reaction conditions generating the major compound thus leading to the formation of only one methyl ether. The ring fission could be visualized as taking place in the quinone stage in which the oxygen link will have ester characteristics.



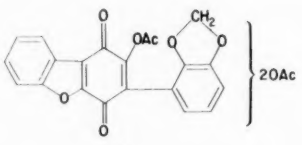
VI



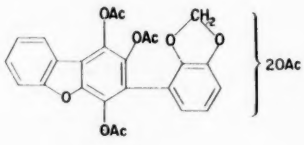
VII

(iii) Acetate and leucoacetate of thelephoric acid:

The formation of a heptamethyl ether indicates the existence of seven hydroxyl groups in the molecule of leucothelephoric acid. But thelephoric acid forms only a triacetate (VIII) and a leucopentaacetate (IX) instead of a pentaacetate and a leucoheptaacetate. This shows that during acetylation and leucoacetate formation, dehydration also takes place involving 5- and 2'-hydroxyl groups, leading to the formation of a furan ring (cf. Read and Vining[2]).



VIII



IX

As already mentioned, similar ring closure may also take place when thelephoric acid (IV) is heated in high vacuum yielding the furan (V). This change also will be facilitated by boiling with acidic reagents like hydriodic acid (cf. Erdtman et al.[7])

(iv) Methylenedioxy groups in thelephoric acid:

Since the above ideas explain satisfactorily the formation of a leucoheptamethyl ether and a leucopentaacetate, our original suggestion[1] that thelephoric acid contains two methylenedioxy groups (formula I) is no more necessary. It seems to contain only one methylenedioxy group and the analytical results (Table 1) also agree with the requirements of the new formulation.

We would like to mention that the test for methylenedioxy group[8,9] is given by thelephoric acid and its derivatives, and that it is markedly prominent in its hydrogen peroxide oxidation products. Apart from the colour reactions, I.R. spectra of thelephoric acid and its derivatives contain bands attributable to the presence of such groups[10] in the regions 1478 - 1465, 1369 - 1328, 1265 - 1263, and 1041 - 1014 cm^{-1}.

Our earlier attempts to demethylenate thelephoric acid with hydriodic acid and acetic anhydride met with difficulties because of the readiness with which the leucocompound separated out. However by prolonged refluxing of thelephoric acid with aqueous hydriodic acid we could finally succeed in

---

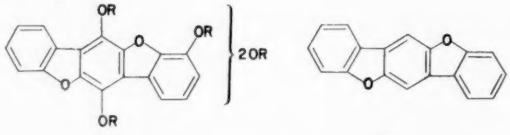
7 H. Erdtman and N.E. Stjernstrom, Acta Chem. Scand. 13, 653 (1959).

8 F. Feigl, Spot Tests in Organic Analysis p. 190. Elsevier, Amsterdam (1956).

9 J. Eisenbeiss and H. Schmid, Helv. Chim. Acta 42, 61 (1959).

10 L.H. Briggs, L.D. Colebrook, H.M. Fales and W.C. Wildman, Analyt. Chem. 29, 904 (1957).

demethylenating it and obtaining the nor-leucothelephoric acid. In this reaction, closure of one furan ring should necessarily have taken place for the reasons mentioned already. Hence the product should give, a heptaacetyl derivative (due to regeneration of 2 hydroxyl groups from the methylenedioxy group) and a heptamethyl ether. But actually it gave only a pentaacetyl derivative and a pentamethyl ether. This showed that demethylenation is also accompanied by a further dehydration resulting probably in a second furan ring closure giving a dioxidoterphenyl of the formula (X, R = H). The I.R. spectrum of the acetate of this compound is different from that of the leucoacetate of thelephoric acid, and also it showed the disappearance of bands due to methylenedioxy group, particularly in the regions 1348 and 1014 cm^{-1}, which were found in the I.R. spectrum of the leucoacetate of thelephoric acid. The U.V. spectrum of the acetate of this compound (X, R = Ac) [λ max and $E_{1cm}^{1\%}$ 2640 (210), 3080 (shoulder) (517), 3200 (960) and 3350 (1065)] seems to resemble that of the dioxidoterphenyl (XI) reported by Gripenberg.[3] The analytical values (Table 1) are also in agreement with this structure. This reaction, besides proving the presence of methylenedioxy group in the molecule, has also enabled us to locate its position as (2":3") in the molecule.



X XI

(v) Attempted fission of thelephoric acid:

There has been considerable difficulty in carrying out potash fusion and oxidative degradations and these have not yielded any fruitful results so far. Alkaline hydrogen peroxide oxidation gave only a trace of acidic

TABLE 1

Analytical Values

S. No.	Name of the compound	Found Values C%	H%	OAc/OMe%	Formula	Calc. Values C%	H%	OAc/OMe%
1.	Thelephoric acid*	60.5	3.0	-	IV, $C_{19}H_{12}O_9$	59.4	3.2	-
	" after heating	61.5	3.3	-	V, $C_{19}H_{10}O_8$	62.3	2.4	-
2.	Triacetate	60.5	3.8	29.4	VIII, $C_{25}H_{16}O_{11}$	61.0	3.3	3 OAc, 26.2
3.	Leucopentaacetate	59.4	3.7	36.7	IX, $C_{29}H_{22}O_{13}$	60.0	3.2	5 OAc, 37.2
4.	Methyl ether (obtained by catalytic reduct.) major component	64.8	5.8	38.8**	VI, $C_{26}H_{28}O_9$	64.5	5.8	7 OMe, 44.8
5.	Methyl ether (obtained by hydrosulphite method)	65.0	5.8	42.8				
6.	nor-leucothelephoric acid methyl ether	67.2	4.8	33.0**	X, R = Me $C_{23}H_{20}O_7$	67.6	4.9	5 OMe, 38.0
7.	nor-leucothelephoric acid acetate.	61.5	3.5	43.9	X, R = Ac $C_{28}H_{20}O_{12}$	61.3	3.7	5 OAc, 39.2

* Found values lie in between those required for formulae IV and V.

** The methoxyl estimations of this and similar compounds sometimes give low values (cf. Kögl et al. Ann. 465, 211 (1928).

components which gave quite vivid colour in the tests for methylenedioxy group. Paper chromatography revealed the presence of at least two acids, but none of them corresponded with piperonylic acid or orthopiperonylic acid.[11] Oxidation of thelephoric acid with lead tetraacetate to convert it into pulvinic acid derivative (cf. atromentin[12] and polyporic acid[13]) were unsuccessful probably because under the acidic conditions used, dehydration is enhanced resulting in the formation of the furan ring which stabilizes the molecule. Further work to locate the position of the other two hydroxyl groups will be undertaken when more material is available and fuller details will be published elsewhere.

We convey our thanks to Professor Jarl Gripenberg of Finland for a specimen of thelephoric acid, and to Mr. M. V. R. Rao of our department for the X-ray spectra.

---

[11] W.H. Perkins, Jr. and V.M. Trikojees, J. Chem. Soc. 2929 (1926).

[12] O.P. Mittal and T.R. Seshadri, Curr. Sci. 26, 4 (1957).

[13] R.L. Frank, G.R. Clark and J.N. Coker, J. Amer. Chem. Soc. 72, 1824 (1950).

Tetrahedron Letters No.16 pp. 11-16, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

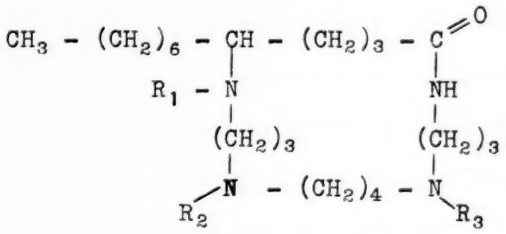
THE STRUCTURE OF PITHECOLOBINE

K. Wiesner and D. E. Orr

Organic Chemistry Laboratory, University of New Brunswick, Fredericton, Canada

(Received 20 June 1960)

SOME time ago we have isolated[1] from the bark of the tree Pithecolobium saman Benth. the alkaloid pithecolobine, $C_{22}H_{46}N_4O_2$. Subsequently, we have shown[2,3] that this compound must be represented by the structures I or II.

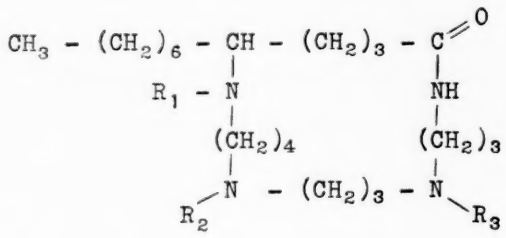


(I)

[1] K. Wiesner, D. M. MacDonald, Z. Valenta and R. Armstrong, Can. J. Chem. 30, 761 (1952).

[2] K. Wiesner, D. M. MacDonald and C. Bankiewicz, J. Am. Chem. Soc. 75, 6348 (1953).

[3] D. E. Orr and K. Wiesner, Chem. and Ind. 672 (1959).



(II)

one of R_1, R_2 or R_3 = OH
remaining two = H

We have now corroborated the formula I by a synthesis of racemic desoxypithecolobine tetratosylate (V). Desoxypithecolobine is a tetrasecondary base[2], $C_{22}H_{48}N_4$ obtainable from pithecolobine by lithium aluminum hydride reduction[1]. The synthesis was performed in analogy to the elegant syntheses of nitrogen containing macrocycles by Stetter[4].

Our starting material was 1,5-dibromododecane[5] which was converted into 1,5-diazidododecane by treatment with sodium azide in diethyleneglycol monomethyl ether as solvent at 95° for 30 hours. The diazide was not characterized but immediately converted into the hygroscopic oily 1,5-diaminododecane by hydrogenation in methanol with platinum oxide (b.p. 95°/0.04 mm outside temperature).

---

[4]H. Stetter and E. E. Roos, Chem. Ber. 87, 566 (1954).

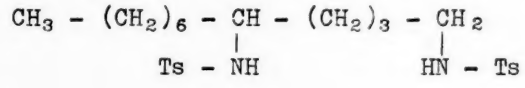
[5]A. Franke and A. Kroupa, Monatsh. 56, 347 (1930).

1960

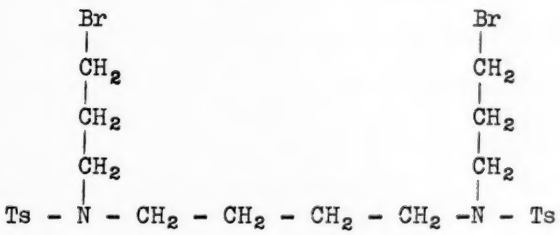
The ditosylate of this compound (III) was a thick syrup which sublimed without decomposition in high vacuo. Found: C, 61.53; H, 7.93; N, 4.96; O, 13.14; S, 11.69. Calc. for $C_{26}H_{40}N_2O_4S_2$: C, 61.39; H, 7.93; N, 5.50; O, 12.58; S, 12.61%.

1,4-Diaminobutane was converted into the ditosylate (m.p. 140°) in the usual manner. Found: C, 54.34; H, 6.04; O, 15.82; N, 7.70; S, 15.89. Calc. for $C_{18}H_{24}N_2S_2O_4$: C, 54.52; H, 6.10; O, 16.14; N, 7.06; S, 16.17%.

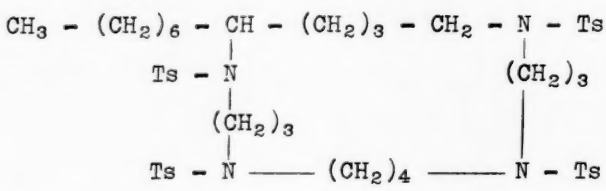
The above compound was converted into the dibromide IV (m.p. 109°) by treatment with 1,3-dibromopropane under the conditions recommended by Stetter[4].



(III)



(IV)



(V)

Found: C, 44.63; H, 5.28; O, 10.42; N, 4.26; S, 9.98; Br, 25.32. Calc. for $C_{24}H_{34}N_2S_2O_4Br_2$: C, 45.14; H, 5.36; O, 10.02; N, 4.39; S, 10.04; Br, 25.03%.

The coupling of the disodium salt of III with the dibromide IV was performed under high dilution in dimethyl formamide according to the directions of Stetter[4]. Compound V was separated from polymeric products by chromatography on alumina. It was eluted as a colorless glass by benzene-ether (1:1). It was rechromatographed and the peak fraction, which showed a constant infrared spectrum on repeated chromatography, was analysed after drying in high vacuo at 95°. Found: C, 61.93; H, 8.11; N, 5.61; O, 12.46; S, 12.13. Calc. for $C_{50}H_{72}N_4O_8S_4$: C, 60.94; H, 7.37; N, 5.69; O, 13.00; S, 13.03%.

The synthetic racemic compound V had an infrared spectrum superimposable on the spectrum of 'natural' desoxypithecolobine tetratosylate both in potassium bromide and in CCl_4 and $CHCl_3$ solution. Also, the NMR spectra of both materials were identical and fully compatible with structure V.

1960

The NMR spectrum of pithecolobine is fully compatible with the formula I. It shows a peak (area 1H) at 1.50 ppm assigned to the hydroxylamine hydroxyl, and a multiplet (area 1H) at 4.68 ppm assigned to the amidic hydrogen. A multiplet centered at 6.65 ppm (area 2H) was assigned to the two hydrogens unshielded by the amidic nitrogen. A multiplet centered at 7.28 ppm (area 11H) was assigned to hydrogens unshielded by the three basic nitrogens. A triplet centered at 7.72 ppm (area 2H) was assigned to the two hydrogens unshielded by the amide carbonyl. A large unresolved peak between 8.43 and 8.57 ppm contained all the remaining hydrogens of I except the $C-CH_3$ group which appeared as a peak between 9 and 9.07 ppm (area 3H).

We have now ascertained by model experiments that diakyl hydroxylamines of the type I remained largely unchanged in the reduction with formic acid-formaldehyde and yield tertiary amine N-oxides by methylation with methyl iodide. Consequently, these two processes would be expected to convert I into a bis quaternary salt N-oxide. The fact that pyrolytic decomposition of this material yields tetramethyltrimethylene diamine and compound VI[2] is very

$$CH_3-(CH_2)_6-CH=CH-(CH_2)_2-\overset{\overset{O}{\|}}{C}-NH-CH_2-CH=CH_2$$

(VI)

easily rationalized if R_3 in formula I is a hydroxyl and R_1 and R_2 are hydrogens.

We wish to thank the Schering Corporation, New Jersey, and Hoffmann-LaRoche Inc., New Jersey for grants which enabled us to carry out this investigation. D.E.O. thanks the National Research Council, Ottawa, for a studentship.

Tetrahedron Letters No.16 pp. 17-20, 1960. Pergamon Press Ltd. Printed in Great Britain

APPORTIONMENTS OF PRODUCTS FROM UNSYMMETRICALLY SUBSTITUTED MESOMERIC CARBONIUM IONS

Jerome A. Berson
Dept. of Chemistry, University of Southern California
Los Angeles 7, Calif.

(Received 18 June 1960)

Beltrame, Bunton and Whittaker[1] have reported that the kinetically controlled mixture of products from the methanolysis (via a carbonium ion) of bornyl chloride (endo-IB, X = Cl, see Table I) isobornyl chloride (exo-IB), and camphene hydrochloride (IA) is rich in the thermodynamically unstable tertiary derivative, camphene hydrate methyl ether (IA-OCH_3), products of the bornyl or isobornyl structure being either entirely absent or found in only small amount. These authors have noted that the presumably similar carbonium ion involved in the reactions of camphene hydrochloride in aprotic solvent[2] (competing exchange of chloride vs. rearrangement to isobornyl chloride) also reacts more rapidly to give product of the camphenehydro structure.

I wish to point out that these are manifestations of a general phenomenon which is of significance to an understanding of the behavior of mesomeric carbonium ions. The generalization may be stated in the following form: Under kinetically controlled circumstances, the carbonium ion intermediate(s) connecting a pair of Wagner-Meerwein related products reacts with nucleophiles predominantly at that one of the two cationic sites which bears the greater number of alkyl substituents. This amounts to Markownikoff-type behavior; like Markownikoff's original rule, the generalization may require modification in special circumstances, e.g., in acyclic systems, when one of the sites bears an unsaturated substituent such as aryl or alkenyl, or when polar substituents (halogen, carboxyl, etc.) are present. The experimental basis for the generalization is given in Table I. As is the case

---

[1] P. Beltrame, C. A. Bunton and D. Whittaker, Chemistry and Industry 557 (1960).

[2] T. P. Nevell, E. de Salas and C. L. Wilson, J. Chem. Soc. 1188 (1939).

with system I, the tertiary bicyclic derivatives II-V are unstable with respect to their secondary isomers under equilibrating conditions. Kinetic control of the products in Table I is assured by the reaction conditions (excess of alkali) and/or by control experiments.

A possible exception to the rule may account for the fact that no tertiary derivative (VIIIA) has been reported to arise from solvolyses of derivatives of the pinyl-bornyl (VIIIA-IB) or pinyl-fenchyl (VIII-IIIB) systems; the two stereoisomeric alcohols of structure VIIIA, for example,

VIIIA

are made by alternate means.[10] Because of the strain involved in generating the bicyclo(3.1.1)heptyl ring system, it seems likely that the carbonium ion intermediates connecting the pairs VIIIA-IB and VIIIA-IIIB would resist attack at the tertiary position.

---

[3] References cited by J. Simonsen and L. N. Owen, "The Terpenes", Vol. II, Cambridge University Press, 1949, p. 355 ff.

[4] H. Meerwein and L. Gérard, Ann. 435, 174 (1924).

[5] N. J. Toivonen, E. Siltanen and K. Ojala, Ann. Acad. Sci. Fennicae Ser. A II, No. 64 (1955).

[6] G. Komppa and S. Beckmann, Ann. 503, 130 (1933); 509, 51 (1934).

[7] P. D. Bartlett, E. R. Webster, C. E. Dills and H. G. Richey, Ann. 623, 217 (1959).

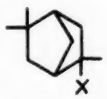
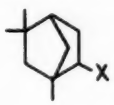
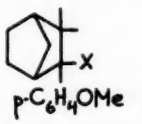
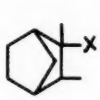
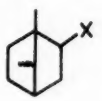
[8] O. Aschan, Öfversigt Finska Vetenskaps-Soc. Förhandl 53 A, No. 8 (1910/11).

[9] S. Winstein, M. Brown, K. C. Schreiber and A. H. Schlesinger, J. Am. Chem. Soc. 74, 1141 (1952).

[10] A. Lipp, Ber., 56, 2098 (1923); O. Wallach, Ann. 356, 239 (1907); W. D. Burrows and R. H. Eastman, J. Am. Chem. Soc. 81, 245 (1959).

TABLE I

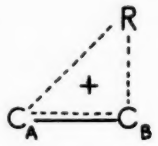
KINETICALLY CONTROLLED PRODUCTS OF SOME CARBONIUM ION REACTIONS

No.	Ref.	Starting material	A	B	Predominant Product
I	1,3,4	C			A
II	5	C			A
III	6	C			A
IV	7	C	 p-C_6H_4OMe	p-C_6H_4OMe	A
V	8	C			A
VI	9	D	$CH_3CHXCH_2C_6H_5$	$CH_3\overset{C_6H_5}{\overset{\vert}{C}}HCH_2X$	A
VII	9	D	$CH_3CHXCH_2p\text{-}C_6H_4OMe$	$CH_3\overset{p\text{-}C_6H_4OMe}{\overset{\vert}{C}}HCH_2X$	A

C = chloride prepared from the corresponding olefin, alcohol, or tricyclene and HCl. D = p-toluenesulfonate solvolysis.

The behavior of allylically mesomeric cations suggests the operation of influences that may be related to those responsible for the pattern of Table I. In kinetically controlled reactions, allylic cations give high or even predominant proportions of products resulting from attack of a nucleophile at the more highly substituted carbon of the allylic system, despite the pronounced thermodynamic preference for the allylically isomeric product, which has the more highly substituted double bond.[11]

The behavior typified by Table I may signify either (i) that the carbonium ion intermediates are unsymmetrically bridged, e.g., IX, or (ii) that the electrical effects of the alkyl groups come into play in the transition states for conversion of the bridged intermediate to products, favoring localization of cationic character at the more highly substituted carbon, C_A.



IX

---

[11] R. H. de Wolfe and W. G. Young, Chem. Revs. 56, 753 (1956).

Tetrahedron Letters No.16, pp. 21-32, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

DARSTELLUNG VON 16-METHYLEN-STEROIDEN DER CORTICOID- UND PROGESTERONREIHE

H.J.Mannhardt, F.v.Werder, K.H.Bork,
H.Metz und K.Brückner
Forschungslaboratorium, E.Merck A.G., Darmstadt

(Received 27 June 1960)

Eine Veröffentlichung von G.Nominé, D.Bertin und A.Pierdet[1] gibt uns Anlaß, über unsere eigenen Arbeiten zur Darstellung von physiologisch interessanten 16-Methylen-steroiden zu berichten.

Das bereits von A.Wettstein[2] dargestellte 16-Methyl-5,16-pregnadien-3β-ol-20-on-acetat (I) wurde mit Wasserstoffperoxyd in methanolisch-alkalischer Lösung nach der Methode von P.L.Julian[3] in 16β-Methyl-16α,17α-oxido-5-pregnen-3β-ol-20-on (IIa; Schmp.185-186°, $[\alpha]_D^{23}$ - 25°[4];

---

1 G.Nominé, D.Bertin und A.Pierdet, Tetrahedron 8, 217 (1960)

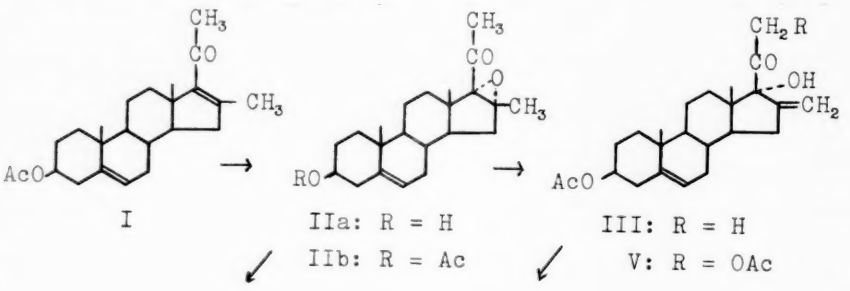
2 A.Wettstein, Helv.chim.acta 27, 1803 (1944)

3 P.L.Julian, E.W.Meyer, W.J.Karpel und I.R.Waller, J.Amer.Chem.Soc. 72, 5145 (1950)

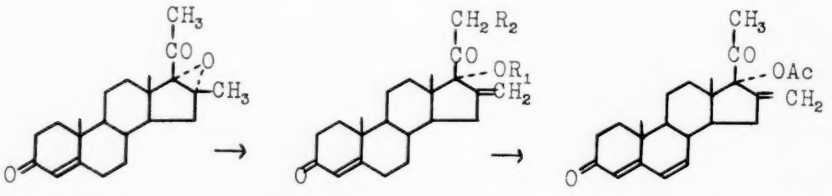
4 Die Schmelzpunkte sind unkorrigiert; die spez. Drehungen wurden, wenn nicht anders angegeben, in Chloroform gemessen; die UV-Spektren wurden in Aethanol als Lösungsmittel aufgenommen.

3-Acetat IIb: Schmp. 178-180°, $[\alpha]_D^{23}$ -12°) übergeführt.

Unter der Einwirkung von Säuren, beispielsweise bei einstündigem Kochen mit katalytischen Mengen p-Toluolsulfonsäure in benzolischer Lösung oder Chlorwasserstoff in Essigsäureäthylester, wurde IIb in hoher Ausbeute zu 16-Methylen-5-pregnen-3β,17α-diol-20-on-3-acetat (III; Schmp. 196-198°, $[\alpha]_D^{23}$ - 140°) isomerisiert.[5]

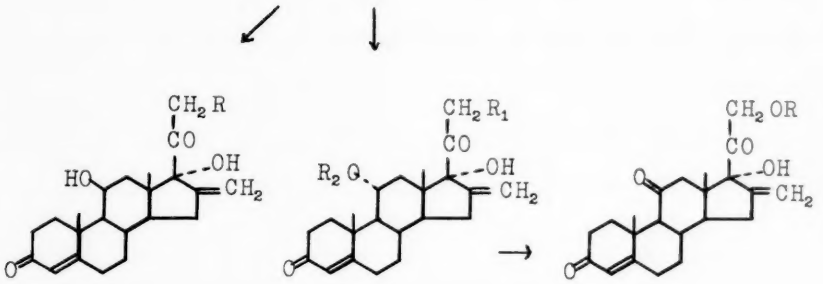


I IIa: R = H IIb: R = Ac III: R = H V: R = OAc



VII VIa: R_1 =H, R_2 = OH VIb: R_1 = H, R_2 = OAc VIII: R_1 = R_2 = H IX: R_1 = H, R_2 = J X: R_1 = Ac, R_2 = H XI

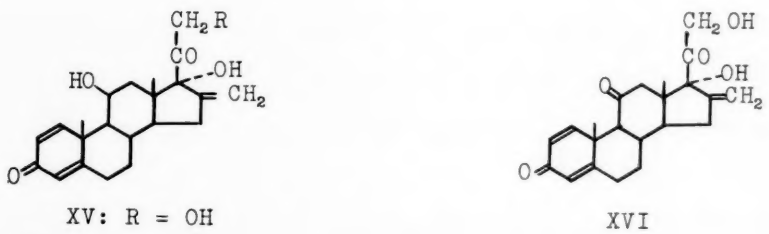
[5] Einer Privatmitteilung der Herren Dr.E.B.Hershberg und Dr.H.L.Herzog zufolge war das 16-Methylen-5-pregnen-3β,17α-diol-20-on-3-acetat (III), mit dem sich unsere Verbindung als identisch erwies, auch in den Laboratorien der Schering Corporation in Bloomfield,N.J. erhalten worden. Wir danken den genannten Herren auch an dieser Stelle für die Bekanntgabe ihrer Ergebnisse.



XIIa: R = OH
XIIb: R = OAc
XVII: R = H

XIIIa: R_1 = OH, R_2 = H
XIIIb: R_1 = OAc, R_2 = H
XIIIc: R_1 = OAc, R_2 = Ts
XXIVa: R_1 = R_2 = H
XXIVb: R_1 = H, R_2 = Ts

XIVa: R = H
XIVb: R = Ac



XV: R = OH
XVIII: R = H

XVI

Dieses überraschende Ergebnis wurde wie folgt bewiesen: 1. die IR-Spektren sowohl von III als allen im Folgenden beschriebenen Verbindungen zeigten die für eine endständige Methylengruppe charakteristische Bande bei 915-925 cm^{-1}; 2. die Ozonisation von III lieferte Formaldehyd, isoliert als Dimedon-Verbindung; 3. der Abbau von III durch

Beckmannsche Umlagerung seines 20-Oxims mit Phosphoroxychlorid in Pyridin[6] führte nahezu quantitativ zu dem von P.L.Julian[7] beschriebenen 16-Methylen-5-androsten-3β-ol-17-on-acetat.

In wenigen Stufen konnte aus III als wichtiges Zwischenprodukt das 16-Methylen-4-pregnen-17α,21-diol-3,20-dion (= 16-Methylen-Reichsteins Substanz S) (VIa) hergestellt werden. So führte die Bromierung von III in Essigsäure-Chloroform mit doppelt molarer Menge Brom zu 5α,6β,21-Tribrom-16-methylen-pregnan-3β,17α-diol-20-on-3-acetat (IV), das ohne Reinigung in Aceton mit Natriumjodid und anschließend mit Kaliumacetat zu 16-Methylen-5-pregnen-3β, 17α,21-triol-20-on-3,21-diacetat (V; Schmp.195-197°, $[\alpha]_D^{23}$ -66°) weiter umgesetzt wurde. (Bei Anwendung der dreifach molaren Menge Brom blieb trotz zusätzlichen Schutzes der exocyclischen Doppelbindung während der Substitution am C-Atom 21 die Ausbeute an V wesentlich geringer.)

Die Einwirkung einer Kultur von Flavobacterium dehydrogenans auf V bewirkte in einer Stufe die Verseifung beider Acetatgruppen, Oxydation der Hydroxylgruppe in 3-Stellung und Isomerisierung der Doppelbindung von 5,6- nach 4,5-Stellung und führte zu 16-Methylen-Reichsteins

---

6 J.Schmidt-Thomé, Liebigs Ann.Chem. 603, 43 (1957)

7 P.L.Julian, E.W.Meyer und H.C.Printy, J.Amer.Chem. Soc. 70, 3872 (1948)

Substanz S (VIa; Schmp.206-207°, $[\alpha]_D^{23}$ + 47,5°, λ_{max}: 240 mμ, ε: 17200).

Die Synthese von VIa wurde unter Umgehung der mikrobiologischen Stufe noch auf einem zweiten Weg durchgeführt:

Dafür wurde IIa nach der Methode von Oppenauer zu 16β-Methyl-16α,17α-oxido-4-pregnen-3,20-dion (VII; Schmp.161°, $[\alpha]_D^{23}$ + 154°, λ_{max}: 240 mμ, ε: 17600) oxydiert und dieses Epoxyd in der bereits beschriebenen Weise, z.B. mit p-Toluolsulfonsäure in Benzol, zu 16-Methylen-17α-hydroxy-4-pregnen-3,20-dion (VIII; Schmp.223°, $[\alpha]_D^{23}$ -7,5°, λ_{max}: 240,5 mμ, ε: 17160) aufgespalten. VIII wurde nach dem Verfahren von H.J.Ringold und G.Stork[8] in 21-Stellung jodiert und das rohe Jodid IX durch Kochen mit Kaliumacetat in Aceton in 16-Methylen-Reichsteins Substanz S-21-acetat (VIb; Schmp. 162-163°, $[\alpha]_D^{23}$ + 51,5°, λ_{max}: 240,5 mμ, ε: 17000) verwandelt, das sich in üblicher Weise zum freien Alkohol VIa verseifen ließ.

Das Zwischenprodukt VIII lieferte bei der Acetylierung der am C-Atom 17 befindlichen Hydroxylgruppe das oral gestagen wirksame 16-Methylen-17α-acetoxy-progesteron (X; Schmp.218-220°, $[\alpha]_D^{23}$: - 56,4°, λ_{max}: 240 mμ, ε: 18200). Bei der Dehydrierung von X mittels Chloranil[9] wurde 6-Dehydro-16-methylen-17α-acetoxy-progesteron (XI; Schmp.226-227°,

---

[8] H.J.Ringold und G.Stork, J.Amer.Chem.Soc. 80, 250 (1958)

[9] E.J.Agnello und G.D.Laubach; J.Amer.Chem.Soc. 79, 1257 (1957)

$[\alpha]_D^{23}$ - 130°, λ_{max}: 281,5 mμ, ε: 27200) erhalten, das wie in analogen Fällen bereits beschrieben eine noch höhere gestagene Wirkung besitzt.[10]

Von 16-Methylen-Reichsteins Substanz S (VIa) aus führte der Weg weiter zu den 16-Methylen-Analoga der Corticosteroidreihe. Zu diesem Zweck wurde VIa mit einer Kultur von Curvularia lunata[11] in 11β-Stellung unter Bildung von 16-Methylen-hydrocortison (XIIa; Schmp. 232-233°, $[\alpha]_D^{23}$ + 79° (Dioxan), λ_{max}: 241 mμ, ε: 17400; 21-Acetat XIIb: Schmp.218-220°, $[\alpha]_D^{23}$ + 90°, λ_{max} 241,5 mμ, ε: 17200) hydroxyliert. Die 11α-Hydroxylierung von VIa zu 16-Methylen-11-epi-hydrocortison (XIIIa, Schmp. 199-201°, $[\alpha]_D^{23}$ + 42° (Dioxan), λ_{max}: 241 mμ, ε : 16700; 21-Acetat XIIIb: amorph) gelang durch Fermentation mit Fusarium equiseti Saccardo.[12] Oxydation von XIIb oder XIIIb in Aceton mit einer wäßrigen Chromsäure-Schwefelsäure-Mischung lieferte 16-Methylen-cortison-acetat (XIVb; Schmp.213-214°, $[\alpha]_D^{23}$ + 140° (Dioxan), λ_{max}: 237 mμ, ε : 16900), das zu 16-Methylen-cortison

---

[10] H.J.Ringold, E.Batres, A.Bowers, J.Edwards und J.Zderic, J.Amer.Chem.Soc. 81, 3485 (1959); H.J.Ringold, J.P. Ruelas, E.Batres und C.Djerassi, J.Amer.Chem.Soc. 81, 3712 (1959); P.B.Sollman, R.L.Elton und R.M.Dodson, J.Amer.Chem.Soc. 81, 4435 (1959); A.Bowers, L.C. Ibanez und H.J.Ringold, J.Amer.Chem.Soc. 81, 5991 (1959)

[11] G.M.Shull und D.A.Kita, J.Amer.Chem.Soc. 77, 763 (1955)

[12] H.J.Mannhardt und H.Metz, Dt.Pat. 1 069 623

(XIVa; Schmp. 219-220°, $[\alpha]_D^{23}$ + 136° (Dioxan), λ_{max}: 237 mμ, ε : 16800) verseift wurde. XIIa wurde durch Bebrüten mit Corynebacterium simplex[13] in 1,2-Stellung zu 16-Methylen-prednisolon (XV; Schmp.233-235°, $[\alpha]_D^{23}$ + 31° (Dioxan), λ_{max}: 243 mμ, ε : 15900) dehydriert. Analog ergab XIVa bei der mikrobiologischen Dehydrierung 16-Methylen-prednison (XVI; Schmp. 218-219°, $[\alpha]_D^{23}$ + 103° (Dioxan), λ_{max}: 238 mμ, ε: 16100).

Die 21-Desoxyverbindungen von XIIa und XV wurden von VIII aus erhalten. Dabei lieferte die Fermentation mit Curvularia lunata das 16-Methylen-4-pregnen-11β,17α-diol-3,20-dion (XVII; Schmp.215-216°, $[\alpha]_D^{23}$ + 42°, λ_{max}: 241 mμ, ε : 17300), das seinerseits durch mikrobiologische 1,2-Dehydrierung mit Corynebacterium simplex in 16-Methylen-1,4-pregnadien-11β,17α-diol-3,20-dion (XVIII; Schmp.238-241°, $[\alpha]_D^{23}$ - 37,5°, λ_{max}: 243,5 mμ, ε: 15400) umgewandelt werden konnte.

Verschiedene Reaktionsfolgen führten zu 9α-Fluor-16-methylen-steroiden. So war das als Analogon zu Dexamethason[14] interessante 9α-Fluor-16-methylen-prednisolon

---

13 A.Nobile, W.Charney, P.L.Perlman, H.L.Herzog, C.C.Payne, M.E.Tully, M.A.Jevnik und E.B.Hershberg, J.Amer.Chem. Soc. 77, 4184 (1955)

14 G.E.Arth, J.Fried, D.B.R.Johnston, D.R.Hoff, L.H. Sarett, R.H.Silber, H.C.Stoerk und C.A.Winter, J.Amer. Chem.Soc. 80, 3161 (1958); E.P.Oliveto, R.Rausser, L.Weber, A.L.Nussbaum, W.Gebert, C.T.Corniglio, E.B. Hershberg, S.Tolksdorf, M.Eisler, P.L.Perlman und M.M. Pechet, J.Amer.Chem.Soc. 80, 4431 (1958)

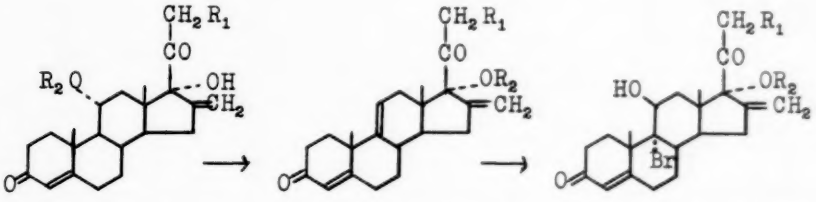
(XXIII) aus XIIIb analog dem Verfahren von J.Fried und E.F.Sabo[15] auf folgendem Weg erhältlich: XIIIb wurde mit p-Toluolsulfochlorid in Pyridin in das 16-Methylen-11-epi-hydrocortison-11-tosylat-21-acetat (XIIIc; Schmp.160-161°, $[\alpha]_D^{23}$ + 67°, λ_{max}: 229 mμ, ε: 24 700) umgewandelt, daraus mittels Natriumacetat p-Toluolsulfonsäure zu 16-Methylen-4,9(11)-pregnadien-17α,21-diol-3,20-dion-21-acetat (XIX; Schmp. 215-217°, $[\alpha]_D^{23}$ + 51°, λ_{max}: 238,5 mμ, ε : 16800) abgespalten, an das sich seinerseits mittels N-Bromsuccinimid in Dioxan-Wasser unter Zusatz einer kleinen Menge Perchlorsäure unterbromige Säure anlagern ließ. Das dabei gewonnene 9α-Brom-16-methylen-hydrocortison-21-acetat (XX) wurde ohne weitere Reinigung mit äthanolischer Kaliumacetatlösung verkocht und das gebildete 9β,11β-Oxido-16-methylen-4-pregnen-17α,21-diol-3,20-dion-21-acetat (XXI; Schmp. 210-211°, $[\alpha]_D^{23}$ - 35° (Dioxan), λ_{max}: 243 mμ, ε : 16200) mit Fluorwasserstoff in Tetrahydrofuranlösung[16] zu 9α-Fluor-16-methylen-hydrocortison-acetat (XXIIb; Schmp.209-211°, $[\alpha]_D^{23}$ + 71°, λ_{max}: 238 mμ, ε : 17300) aufgespalten. Nach Verseifung resultierte 9α-Fluor-16-methylen-hydrocortison (XXIIa; Schmp.242-244°, $[\alpha]_D^{23}$ + 80° (Dioxan), λ_{max}: 238 mμ, ε: 17600), das mikrobiologisch mit Corynebacterium simplex zu 9α-Fluor-16-methylen-prednisolon

---

15 J.Fried und E.F.Sabo, J.Amer.Chem.Soc. 79, 1130 (1957)

16 R.F.Hirschmann, R.Miller, J.Wood und R.E.Jones, J.Amer.Chem.Soc. 78, 4956 (1956)

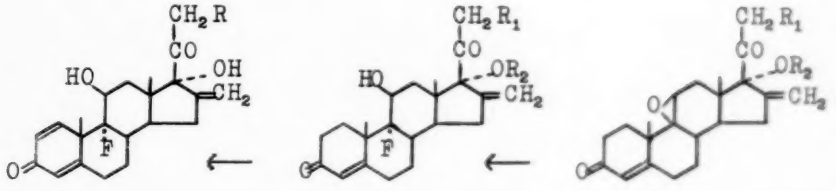
(XXIII; Schmp. 249-251°, $[\alpha]_D^{23}$ + 29° (Dioxan), λ_{max}: 238,5 mμ, ε : 16000) dehydriert wurde.



XIIIa: R_1 =OH, R_2 =H
XIIIb: R_1 =OAc, R_2 =H
XIIIc: R_1 =OAc, R_2 =Ts
XXIVa: R_1 = R_2 =H
XXIVb: R_1 =H, R_2 =Ts

XIX: R_1 =OAc, R_2 =H
XXVa: R_1 = R_2 =H
XXVb: R_1 =H, R_2 =Ac

XX: R_1 =OAc, R_2 =H
XXVI: R_1 =H, R_2 =Ac



XXIII: R=OH
XXIX: R=H

XXIIa: R_1 =OH, R_2 =H
XXIIb: R_1 =OAc, R_2 =H
XXVIII: R_1 = R_2 =H
XXX: R_1 =H, R_2 =Ac

XXI: R_1 =OAc, R_2 =H
XXVIIa: R_1 = R_2 =H
XXVIIb: R_1 =H, R_2 =Ac

In einem zweiten Weg zu XXIII wurde 16-Methylen-17α-hydroxy-progesteron (VIII) mikrobiologisch mit Fusarium equiseti Saccardo in 16-Methylen-4-pregnen-11α,17α-diol-3,20-dion (XXIVa; Schmp.208-210°, $[\alpha]_D^{23}$ - 8°, λ_{max}: 241 mμ,

ε : 16500) umgewandelt. Das 11-Tosylat (XXIVb; Schmp. 162°, $[\alpha]_D^{23}$ - 2°, λ_{max}: 229,5 mμ, ε : 25400) ergab bei der alkalischen Abspaltung von p-Toluolsulfonsäure 16-Methylen-4,9(11)-pregnadien-17α-ol-3,20-dion (XXVa; Schmp. 227-228°, $[\alpha]_D^{23}$ - 23°, λ_{max}: 238,5 mμ, ε : 18000), das nach H.J. Ringold und G.Stork[8] in das 21-Jodderivat übergeführt und direkt weiter mit Kaliumacetat in Acetonlösung zu dem oben beschriebenen XIX verkocht wurde.

Die 21-Desoxyverbindungen von XXII und XXIII waren von XXVa aus zugänglich. An XXVa ließ sich unterbromige Säure in 9,11-Stellung nur mit sehr schlechten Ausbeuten anlagern, da die Reaktion zu einem erheblichen Teil an der exocyclischen Doppelbindung in 16 angreift. Die Reaktion ließ sich aber in die gewünschte Richtung steuern, wenn die 17α-Hydroxylgruppe vor der Anlagerung unter den dafür üblichen Bedingungen acetyliert wurde. Das dabei erhaltene 16-Methylen-4,9(11)-pregnadien-17α-ol-3,20-dion-acetat (XXVb; Schmp. 232-235°, $[\alpha]_D^{23}$ - 64° (Dioxan), λ_{max}: 238,5 mμ, ε : 17800) wurde mit N-Bromsuccinimid und Perchlorsäure in Dioxan-Wasser in 9α-Brom-16-methylen-4-pregnen-11β,17α-diol-3,20-dion-17-acetat (XXVI) übergeführt, aus dem ohne weitere Reinigung Bromwasserstoff zu 9β,11β-Oxido-16-methylen-17α-acetoxy-progesteron (XXVIIb; Schmp. 194-196°, $[\alpha]_D^{23}$ - 142,6° (Dioxan), λ_{max}: 242 mμ, ε : 15800) abgespalten wurde. Das nach Verseifung erhaltene 9β,11β-Oxido-16-

1960

methylen-4-pregnen-17α-ol-3,20-dion (XXVIIa; Schmp. 172-175°, $[\alpha]_D^{23}$ - 122,6°, λ_{max}: 243 mμ, ε : 14200) wurde mit Fluorwasserstoff in Tetrahydrofuran zu 9α-Fluor-16-methylen-4-pregnen-11β,17α-diol-3,20-dion (XXVIII; Schmp. 247-250°, $[\alpha]_D^{23}$ + 53° (Aethanol), λ_{max}: 238,5 mμ, ε : 18000) aufgespalten und ging bei mikrobiologischer Dehydrierung mit Corynebacterium simplex in 9α-Fluor-16-methylen-1,4-pregnadien-11β,17α-diol-3,20-dion (XXIX; Schmp. 271-275°, $[\alpha]_D^{23}$ + 30° (Aethanol), λ_{max}: 238,5 mμ, ε : 15800) über.

Als Verbindung mit acetylierter 17α-Hydroxylgruppe und hoher oraler gestagener Wirkung ist noch das durch Fluorwasserstoff-Aufspaltung von XXVIIb erhältliche 9α-Fluor-16-methylen-4-pregnen-11β,17α-diol-3,20-dion-17-acetat (XXX; Schmp. 243-245°, $[\alpha]_D^{23}$ - 32°, λ_{max}: 238 mμ, ε : 18600) zu erwähnen.

Von den neu gewonnenen 16-Methylen-steroiden zeigen einige im Tierversuch eine bemerkenswerte Wirksamkeit. Z.B. besitzen in der Corticoidreihe 16-Methylen-prednisolon (XV), 16-Methylen-prednison (XVI) und 9α-Fluor-16-methylen-prednisolon (XXIII) im Vergleich zu ihren in 16-Stellung unsubstituierten Stammsubstanzen eine verstärkte glucocorticoide Wirksamkeit. Das gleiche gilt für die gestagene Wirkung von 16-Methylen-17α-acetoxy-progesteron (X), 6-Dehydro-16-methylen-17α-acetoxy-progesteron (XI) und 9α-Fluor-16-methylen-11β-hydroxy-17α-acetoxy-

progesteron (XXX). Einzelheiten über die pharmakologischen Eigenschaften der neuen Substanzen werden an anderer Stelle veröffentlicht werden.

Wir danken Herrn Dr.Hampel für die Aufnahme und Deutung der UV- und IR-Spektren.

1960

196

Tetrahedron Letters No.17, pp. 1-4, 1960. Pergamon Press Ltd. Printed in Great Britain.

1960

THE STEREOSPECIFIC TOTAL SYNTHESIS OF dl-8β-CARBOMETHOXY-13-OXOPODOCARPANE, A DEGRADATION PRODUCT OF PHYLLOCLADENE

R. F. Church,[1] R. E. Ireland and J. A. Marshall[2]

Department of Chemistry, The University of Michigan

Ann Arbor, Michigan

(Received 22 June 1960)

MUCH of the work on the structure and stereochemistry of the diterpenoid hydrocarbon phyllocladene has centered around its degradation to 8β-carbomethoxy-13-oxopodocarpane(XI)[3,4]. Hence not only would the synthesis of this keto ester be of intrinsic value itself as corroboration of the degradative work but this keto ester also offers a very attractive intermediate for further elaboration to phyllocladene itself. We should like to report here a stereospecific total synthesis of the keto ester (XI).

Base catalyzed condensation of m-methoxybenzaldehyde with isopropyl methyl ketone led to the unsaturated ketone (I) (84%) b.p. 102-103°/0.08 mm. When this ketone was treated with 1-diethylamino-3-pentanone methiodide in the presence of sodium methoxide, it was converted to the dienone(II), b.p.

---

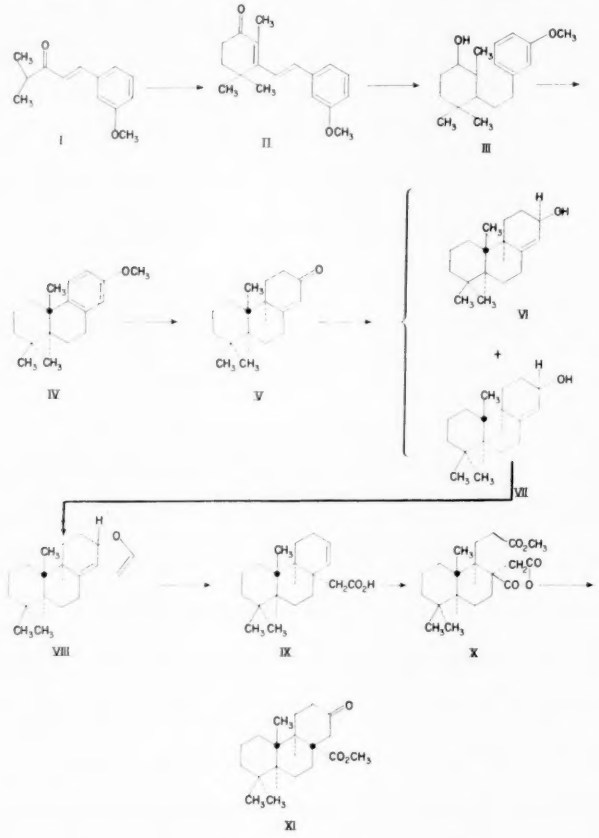
[1] Sun Oil Fellow, 1958-1960.

[2] Public Health Service Research Fellow of the National Heart Institute.

[3] L. H. Briggs, B. F. Cain, B. R. Davis and J. K. Wilmhurst, Tetrahedron Letters No. 8, 8 (1959).

[4] P. K. Grant and R. Hodges, Tetrahedron 8, 261 (1960).

163-167°/0.1 mm λ_{max}^{EtOH} 313mμ(ε15,800) in 40% yield. Catalytic hydrogenation



of this dienone over 10% palladium on carbon in acetic acid led to a saturated ketone b.p. 110°/0.03 mm (bath temp.) (C,78.61%; H,9.54%) which was reduced further with lithium aluminum hydride to the alcohol(III) b.p. 105°/0.03 mm (bath temp.) (82% overall) (C,78.40%; H,10.27%). On treatment of this alcohol with polyphosphoric acid at 85° for 45 min cyclization occurred affording the ether(IV), m.p. 86-88° (C,83.80%;H,10.22%). This crystalline tricyclic material was accompanied by substantial quantities of an oily isomer which may be the cis-fused ring system. That the crystalline tricyclic ether was

1960

indeed trans-locked was shown by the fact that on reduction with lithium in ammonia and subsequent acid hydrolysis an α,β-unsaturated ketone(V), m.p. 92-93.5° (79%)λ_{max}^{EtOH} 242 mμ(ε15,900), was obtained which was identical with the ketone obtained by following the synthetic scheme of Barltrop and Rogers.[5]

Reduction of the unsaturated ketone(V) resulted in the isolation of two epimeric alcohols(VII) and (VI). The former (VII) m.p. 126.5-127.5°, (C,82.33%; H,11.19%) was isolated in 76% yield and the latter (VI) m.p. 109.5-111° (C,82.66%; H, 11.21%) in 20% yield. The close similarity of the behavior of this ketone to cholestenone on chemical reduction[6] coupled with the fact that the less proponderant, lower-melting alcohol was eluted from a Florisil column first indicated that the lower melting isomer possessed the quasi-axial hydroxyl group. Accordingly the more proponderant, higher-melting isomer(VII) was assigned the desired quasi-equatorial conformation and was converted to the vinyl ether (VIII) (80%) m.p. 45.5-46.5° (C,83.24%; H, 10.88%) by equilibration[7] with ethyl vinyl ether in the presence of mercuric acetate. Pyrolysis[8] of this vinyl ether(VIII) at 195° for four hours afforded an aldehyde, b.p. 105°/0.02 mm (bath temp.) (95%) (C,82.96%; H, 10.99%) which on oxidation with silver oxide[9] gave the corresponding acid (IX), m.p. 150-152° (88%) (C,78.63%; H,10.13%; N.E. = 278). Further

---

5 J. A. Barltrop and N. A. Rogers, J. Chem. Soc. 2566 (1958).

6 Pl. A. Plattner, H. Heusser and A. B. Kulkarin, Helv. Chim. Acta 32, 265 (1949).

7 W. H. Watenabe and L. E. Conlon, J. Amer. Chem. Soc. 79, 2828 (1957).

8 A. W. Burgstahler and I. C. Nordin, J. Amer. Chem. Soc. 81, 3151 (1959).

9 K. J. Clark, G. I. Fray, R. H. Jaeger and R. Robinson, Tetrahedron 6, 217 (1959).

oxidation of the unsaturated acid according to the conditions of Lemieux and Rudloff[10] followed by treatment of the resulting crude triacid with firs thionyl chloride and then, methanol in the presence of one-equivalent of pyridine yielded the anhydride-ester (X) b.p. 140°/0.03 mm (bath temp.) (62% yield) (C,68.11%; H,8.58%) λ_{max}^{film} 5.78 μ(ester CO); 5.39 μ, 5.62 μ (strained anhydride CO). The final steps were accomplished by treatment of the anhydride-ester(X) with sodium methoxide in benzene, hydrolysis and decarboxylation of the resulting crude β-keto ester, and esterification of the acid thus obtained with diazomethane. This led to a 35% overall yield of the keto ester(XI) m.p. 135-137° (C,74.52%; H,9.91%). Comparison of the infrared spectrum of this material with that of an authentic sample of 8β-carbomethoxy-13-oxopodocarpane showed them to be identical. The confirmatio thus afforded the structure of the keto ester(XI) places the structure of phyllocladene on a firm footing. The conversion of the keto ester(XI) to phyllocladene itself is being actively pursued.

We gratefully acknowledge the assistance of the Research Corporation in making this work possible. We are especially grateful to Prof. L. H. Briggs for making available to us an authentic sample of the keto ester(XI) and to the Parke, Davis and Co. spectrographic laboratory for measuring the infrared spectra. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Michigan.

---

[10] R. E. Lemieux and E. von Rudloff, Canad. J. Chem. 33, 1701 (1955).

Tetrahedron Letters No.17, pp.5-8, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

BUTIN-(2)-DIOL-(1.4)-POLYMETHYLENÄTHER

W. Treibs und R. Pester

Institut für Organische Chemie der

Universität Leipzig

(Received 28 June 1960)

RUZICKA u. Mitarb.[1], Blomquist u. Mitarb.[2] und Prelog u. Mitarb.[3] synthetisierten Cycloalkine durch Einführung der Dreifachbindung in bereits vorhandenef Ringsysteme. Das stark gespannte Cyclooctin ist die kleinste auf diese Weise dargestellte cyclische Acetylenverbindung, während durch Ringschluß von Kettenalkinderivaten nur spannungsfreie, größere Ringe erhalten werden konnten. Cram u. Mitarb.[4] stellten als kleinstes Ringsystem einen Zwölfring durch Acyloincyclisierung von Decin-(5)-dicarbonsäureester-(1.10) dar.

Ausgehend von Butin-(2)-diol-(1.4) erhielten wir einen Vertreter der noch unbekannten Butin-(2)-diol-(1.4)-polymethylenäther (I), die als Ansaverbindungen und Analoga der Hydrochinon-polymethylenäther (II) von Lüttringhaus[5] angesprochen werden können.

---

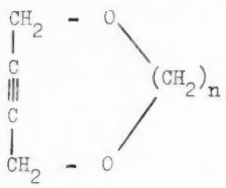
1 L. Ruzicka u. Mitarb., Helv. Chim. Acta 16, 498 (1933).

2 A. T. Blomquist u. Mitarb., J. Amer. Chem. Soc. 73, 5510 (1951); 74, 3636 (1952); 75, 2153 (1953).

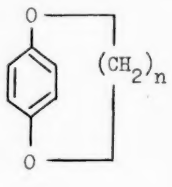
3 V. Prelog u. Mitarb., Helv. Chim. Acta 35, 1598 (1952); 36, 471 (1953); 38, 1776, 1786 (1955); 40, 816 (1957).

4 D. J. Cram u. Mitarb., J. Amer. Chem. Soc. 78, 2518 (1956).

5 A. Lüttringhaus, Liebigs Ann. 528, 181 (1937).



I



II

Die Synthese von I erfolgte in zwei Stufen:

(1) Durch Umsetzung der Mono-natrium-Verbindung des Butin-(2)-diols-(1.4) (1 Mol) mit α.ω-Dibromalkan (5 Mol) in Gegenwart von überschüssigem Butin-(2)-diol-(1.4) (2 Mol) bei 80° entstanden in 20-25%iger Ausbeute die Butin-(2)-diol-(1.4)-mono-(ω-bromalkyl-)äther III (n = 4.6), die als Methyläther (IV) charakterisiert wurden,

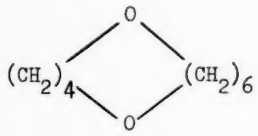
$$HO\text{-}CH_2\text{-}C{\equiv}C\text{-}CH_2\text{-}O\text{-}(CH_2)_n\text{-}Br \qquad III$$

$$HO\text{-}CH_2\text{-}C{\equiv}C\text{-}CH_2\text{-}O\text{-}(CH_2)_n\text{-}OCH_3 \qquad IV$$

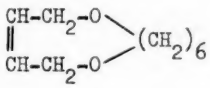
(2) Die cyclisierende Verätherung von III (n = 6)-ein Ringschluß von α-Brom-ω-hydroxyverbindungen zu höhergliedrigen cyclischen Äthern, der u.W. in der Literatur bisher noch nicht beschrieben ist - erfolgte nach dem Verdünnungsprinzip durch langsames Eintropfen in eine siedende, gerührte Suspension von Kaliumhydroxyd in Dioxan. Der Butin-(2)-diol-(1.4)-hexamethylenäther I (n = 6, Ausbeute 15-18%), weiße Nadeln, (aus Methanol vom F = 59,5 - 60°) von schwachen, campherähnlichen Geruch, verflüchtigt sich schnell beim Liegen an der Luft.

Bei der Hydrierung von I (n = 6) in Gegenwart von Adams- bzw. Lindlar-Katalysator entstanden Butandiol-(1.4)- bzw. cis-Buten-(2)-diol-(1.4)-hexamethylenäther (V u. VI).

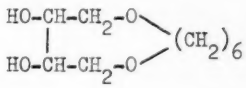
Oxydation von VI mit Osmium (VIII)-oxyd ergab das cis-Glykol VII (Schmp. 109-109,5°; Di-p-nitrobenzoylester, Schmp. 122-122,5°).



V



VI

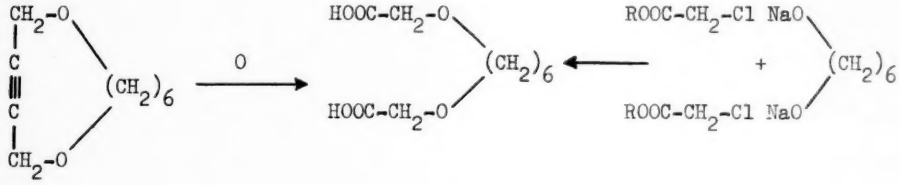


VII

Der Strukturbeweis von I (n = 6) wurde durch oxydative Ringspaltung mit Kaliumpermanganat in Aceton bei -5° zur 2,9-Dioxadecandicarbonsäure-(1,10)

	Schmp. °	Sdp. °/mm	n_D^{65}
I(n=6)	59,5-60	40-50/0,01 (subl.)	1,4696
V	31,5-32	56-56,5/1,2	1,4458
VI	flüssig	60/1,1	1,4618

(VIII; Schmp. 92-93°; Diphenacylester, Schmp. 82-83°) erbracht, die in Analogie zu der von Nerdel u. Rothe[6] beschriebenen 3.8-Dioxasebazinsäure auch synthetisch dargestellt werden konnte.



VIII

Die Hydration der Dreifachbindung mit einer Suspension von Quecksilber-(II)-sulfat in Wasser, welche bei den acyclischen Butin-(2)-diol-(1.4)-dialkyläthern sehr leicht verläuft, gelang nicht.

---

[6] F. Nerdel u. J. Rothe, Chem. Ber. 89, 73 (1956).

Die IR-Spektren der Verbindungen I (n = 6), V und VI zeigen bei 1070-1140 cm^{-1} die sehr intensive C-O-Valenzschwingung. Eine Zuordnung der C≡C-Valenzschwingung bei I (n=6) war infolge der Oberschwingungen im betreffenden Gebiet nicht möglich. Die C=C-Valenzschwingung des Olefins VI findet sich als schwache Bande bei 1662 cm^{-1}. Von den drei Ringverbindungen zeigt nur I (n = 6) bei 470 und 662 cm^{-1} zwei starke Banden, die mit der Ansastruktur im Zusammenhang stehen dürften.

Butin-(2)-diol-(1.4)-mono-ω-brombutyl-)äther III, (n = 4) ließ sich nicht zum entsprechenden Zehnring cyclisieren. Auch Cram u. Mitarb.[4] erhielten bei der bezüglich der Ringgliederzahl analogen Acyloincyclisierung des Octin-(4)-dicarbonsäureesters-(1.8) keine Ringverbindung, sodaß die minimale Gliederzahl für einen solchen Ringschluß bei 11-12 liegen dürfte.

Tetrahedron Letters No.17, pp. 9-11, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

A NOVEL PREVOST REACTION

L. H. Briggs, B. F. Cain and B. R. Davis

Department of Chemistry, University of Auckland, New Zealand

(Received 29 June 1960)

ISOPHYLLOCLADENE, whose formulation as Ia is now secure,[1] undergoes a novel reaction with silver iodobenzoate (Prévost's reagent[2]). This complex normally reacts with olefins to produce the corresponding glycol dibenzoate[3] but when isophyllocladene in dry, refluxing benzene was treated with iodine and silver benzoate it gave, in high yield, an unsaturated monobenzoate, m.p. 161-163° (Found: C, 82.3, 82.3; H, 9.4, 9.0. $C_{27}H_{36}O_2$ requires C, 82.6; H, 9.2. Infra-red bands at 1709 and 853 cm^{-1}) which we now show to possess structure Ib. On hydrolysis Ib afforded the alcohol (Ic), m.p. 126-127° (Found: C, 83.2; H, 11.0. $C_{20}H_{32}O$ requires: C, 83.3; H, 11.2. Infra-red bands at 3279, 1015 and 837 cm^{-1}) which in refluxing acetic anhydride gave the acetate (Id), m.p. 37-38° (Found: C, 79.9; H, 10.4. . $C_{22}H_{34}O_2$ requires: C, 79.9; H, 10.4. Infra-red bands at 1745 and 841 cm^{-1}) and with benzoyl chloride in refluxing pyridine reformed Ib.

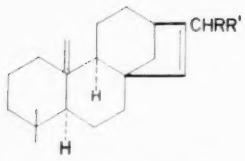
On oxidation with chromium trioxide-pyridine Ic affords the α β-unsaturated aldehyde (Ie), m.p. 125-127°, in almost quantitative yield [Found: C, 84.2;

---

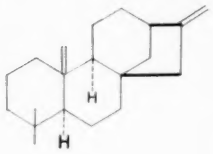
[1] L. H. Briggs, B. F. Cain and R. C. Cambie, Tetrahedron Letters No. 8, 17 (1959) and references there cited; P. K. Grant and R. Hodges, Tetrahedron 8, 261 (1960).

[2] C. V. Wilson in Adams' Org. Reactions IX, 350 (1957).

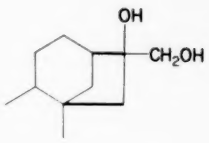
[3] K. B. Wiberg and K. A. Saegebarth, J. Amer. Chem. Soc. 79, 6256 (1957).



I a R=R'=H
b R=H, R'=OBz
c R=H, R'=OH
d R=H, R'=OAc
e RR'=O
f RR'=N.NH.CO.NH$_2$



II



III

H, 10.2. $C_{20}H_{30}O$ requires: C, 83.9; H, 10.6. Infra-red bands at 2817, 2717, 1681, 1597 and 856 cm^{-1} λ_{max}^{EtOH} 253 and 258 mμ (log ε 3.87 and 3.88)]. The long wavelength of these bands [cf. cyclopent-1-enealdehyde λ_{max}^{EtOH} 237-238 mμ (log ε 4.13)][4] is probably an indication of strain in the bicylo [3:2:1] octane system.[5,6] The aldehyde yielded a semicarbazone (If), m.p. 262-264° [Found: C, 73.6; H, 9.6. $C_{21}H_{33}ON_3$ requires: C, 73.4; H, 9.7. λ_{max}^{EtOH} 275.5 mμ (log ε 4.54) and a 2,4-dinitrophenylhydrazone, m.p. 234° [Found: C, 67.5; H, 7.2; N. 12.0. $C_{26}H_{34}O_4N_4$ requires C, 66.9; H, 7.4; N, 12.0. λ_{max}^{EtOH} 234, 255, 291 and 384 mμ (log ε 4.32, 4.32, 4.18 and 4.51)].

That these structural assignments are correct was shown in three ways. On oxidation with selenium dioxide phyllocladene (II) or isophyllocladene gave the aldehyde (Ie) (identified by m.p. and mixed m.p.; semicarbazone identified by m.p. and mixed m.p.) while the semicarbazone (If), on Wolff-Kishner reduction, gave phyllocladene (identified by m.p., mixed m.p., infra-red spectrum). These reactions constitute the first conversion of isophyllo-

---

[4] J. B. Brown, H. B. Henbest and E. R. H. Jones, J. Chem. Soc. 3634 (1950).

[5] R. N. Moore and G. S. Fisher, J. Amer. Chem. Soc. 78, 4362 (1956).

[6] W.Bottomley, A.R.H. Cole and D.E. White, J. Chem. Soc. 2624 (1955).

cladene to phyllocladene. Finally, the diol (III),[7] obtained by oxidation of phyllocladene, on treatment with benzoyl chloride in refluxing pyridine underwent simultaneous dehydration and benzoylation to yield the benzoate (Ib) (identified by m.p. and mixed m.p.).

1960

When the variant of the Prévost reaction developed by Woodward and Brutcher[8] was employed, the same allylic oxidation occurred. Isophyllocladene in moist acetic acid was treated with iodine and silver acetate. The reaction product, on hydrolysis, then yielded the alcohol (Ic) (identified by m.p. and mixed m.p.).

Finally, phyllocladene, in dry benzene, when treated with silver benzoate and iodine also gave the benzoate (Ib). This unexpected result was explained by subsequently finding that phyllocladene is isomerized to isophyllocladene by a trace of iodine in benzene.

Acknowledgements - We gratefully acknowledge assistance from the Chemical Society, the Rockefeller Foundation of New York, the Australian and New Zealand Association for the Advancement of Science and the Research Grants Committee of the University of New Zealand and two of us (B.F.C. and B.R.D.) the award of Research Fund Fellowships.

---

[7] C. W. Brandt, New Zealand J. Sci. Tech. 34 B, 46 (1952).

[8] R. B. Woodward and F. V. Brutcher, Jr., J. Amer. Chem. Soc. 80, 209 (1958).

Tetrahedron Letters No.17, pp. 12-16, 1960. Pergamon Press Ltd. Printed in Great Britain

ON THE REACTION MECHANISM OF THE ETHYLENE POLYMERIZATION WITH HETEROGENEOUS ZIEGLER-NATTA CATALYSTS

P. Cossee

KONINKLIJKE/SHELL-LABORATORIUM, AMSTERDAM

(Shell Internationale Research Maatschappij N.V.)

(Received 4 June 1960)

IN many of the current theories on the mechanism of Ziegler-Natta polymerizations two metal ions bound in a complex are supposed to be required; one to accommodate the monomer molecule, the other carrying the alkyl group. In this way Bier [1] and Gumboldt et al.[2] need two aluminium ions, Natta,[3] Uelzmann [4] and Patat and Sinn [5] use a titanium and an aluminium ion while de Bruyn [6] assumes the reaction to occur at a partly alkylated surface of $TiCl_3$ between two neighbouring titanium ions.

We start from the supposition that the essential reaction occurs at one Ti-ion on account of the general feeling that the presence of unfilled d-orbitals in transition elements, which are responsible for a number of

---

[1] G. Bier, Kunststoffe 48, 354 (1958).
[2] A. Gumboldt and H. Schmidt, Chem. Ztg. 83, 636 (1959).
[3] G. Natta, J. Inorg. & Nuclear Chem. 8, 589 (1958).
[4] H. Uelzmann, J. Polymer Sci. 32, 457 (1958).
[5] F. Patat and H. Sinn, Angew. Chem. 70, 496 (1958).
[6] P.H. de Bruyn, Chem. Weekblad 56, 161 (1960).

1960

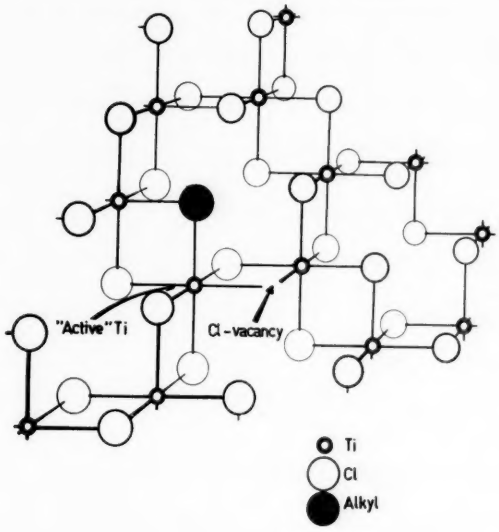
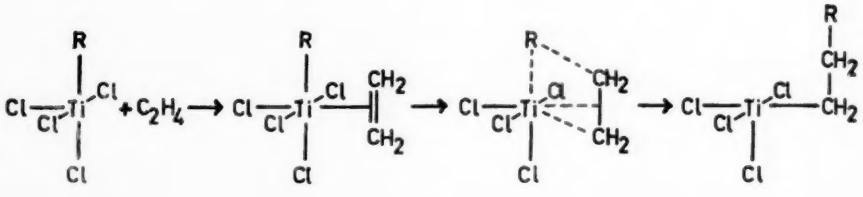


Fig. 1 Schematic drawing of α-$TiCl_3$ lattice with "active center" on the surface

characteristic physical properties, will also be responsible for their catalytic activity. An active center is thus defined as a Ti-ion in the surface layer of a $TiCl_3$ lattice of which one surface Cl-atom is replaced by an alkyl group R while an adjacent Cl-atom has been completely removed in order to accommodate the monomer molecule. This situation is shown in Fig. 1 and is supposed to be the result of the reaction of solid $TiCl_3$ with Al-alkyls. The role of the Al-alkyl is thus primarily an alkylating and reducing one.

The polymerization reaction may now proceed as follows:



After this step the active center retains a Ti-alkyl bond and a vacancy which have, however, mutually changed place. The process may now repeat itself by insertion of the next monomer molecule into the new Cl-vacancy.

Since in the transition state both alkyl group and reacting monomer molecule are attached to the same Ti-ion, only very slight displacements of the nuclei are involved in the propagation step which may be mainly described as an electronic rearrangement.

During the reaction the Al-alkyl may be important as chain-transfer agent and further in termination reactions, in reestablishing lost active centers and as a scavenger, but it is not essential for the propagation. This idea that the essential reaction occurs at one alkylated Ti-ion has already been put forward by Ludlum [7] and has been suggested by Ziegler.[8] The assumption is strongly supported by recent polymerization experiments of Beermann and Bestian.[9]

In conjunction with a few theoretical arguments hitherto not explicitly taken into account the proposed mechanism permits to explain a number of facts not covered by the existing ones.

a) It provides a better insight into the driving force of the reaction. Chatt and Duncanson [10] in 1953 proposed the π-type of bonding between transition metals and olefins. Since this hypothesis was confirmed by

---

[7] D.B. Ludlum, A.W. Anderson and C.E. Ashby, J.Am.Chem.Soc. 80, 1380 (1958).

[8] K. Ziegler, Int. Conf. on Coord. Chem. London 1959, The Chem. Soc. Spec. Publ. 13, 1 (1959).

[9] C. Beermann and H. Bestian, Angew. Chem. 71, 618 (1959).

[10] J. Chatt and L.A. Duncanson, J. Chem. Soc. 2939 (1953).

1960

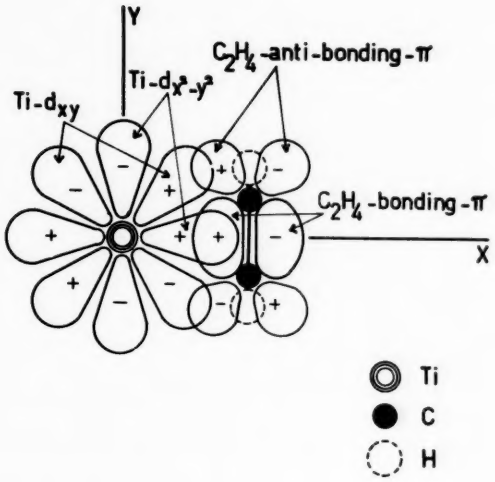


Fig. 2 The π-bond between Ti and C_2H_4.
Electron densities of the orbitals are schematically indicated

X-ray analysis for one of the more stable Pt-olefin complexes,[11] we must assume that also between Ti-ions and ethylene a π-bond is formed. Such a bond is shown in Fig. 2. Its characteristic features are the position of the ethylene molecule perpendicular to the free valency of the metal ion, which allows the π-electrons of the olefin to be used in the σ-bond formation with the $d_{x^2-y^2}$-orbital of the metal, and the possibility of overlap of the d_{xy}-orbital of the metal with the antibonding orbital of the olefin. The latter kind of interaction has an important influence on the energy level scheme of the system, particularly on the situation of the metal d-orbitals of t_{2g}-type. In the combination Ti-ethylene this results in a

---

[11] P.R.H. Alderman, P.G. Owston and J.M. Row, Acta Cryst. 13, 149 (1960).

decrease of the distance between the highest filled bonding orbital and the empty or nearly empty t_{2g}-level. Chatt and Shaw [12] have made it plausible that a small energy difference between filled and empty levels facilitates radical breaking of the σ-bonds of the system as a result of an easy promotion of electrons from the bonding levels to the suppressed t_{2g}-orbital. It therefore appears that the formation of the π-bond between titanium and ethylene is accompanied by a weakening of the already very labile titanium-alkyl bond, thus facilitating the migration of the alkyl group.

We assume that this is the way in which a transition element ion with empty or nearly empty d-orbitals functions as a catalyst in olefin polymerizations.

b) From the above considerations it will be clear that in order to show the desired catalytic effect the empty d-orbitals of the metal must be large enough to overlap sufficiently with the antibonding orbitals of the olefin. Therefore only ions with a comparatively low effective nuclear charge are expected to be good catalysts. This is approximately equivalent to Natta's statement [13] that metals with an ionization potential of the first electron smaller than 7 eV are particularly suited. The unique position of Ti may thus be explained from the size of the t_{2g}-orbitals in close-packed Cl-lattices and may possibly be related to the antiferromagnetic properties of α-$TiCl_3$.

c) The third and perhaps most striking consequence of the mechanism presented is the natural explanation for the formation of isotactic material when propylene is polymerized under the influence of α-$TiCl_3$ and Al-alkyls. This aspect will be treated in a separate letter.[14]

---

[12] J. Chatt and B.L. Shaw, J. Chem. Soc. 705 (1959).

[13] G. Natta, Angew. Chem. 68, 393 (1956).

[14] P. Cossee, Tetrahedron Letters No. 17, 17 (1960).

Tetrahedron Letters No.17, pp. 17-21, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

THE FORMATION OF ISOTACTIC POLYPROPYLENE UNDER THE INFLUENCE OF ZIEGLER-NATTA CATALYSTS

P. Cossee

KONINKLIJKE/SHELL-LABORATORIUM, AMSTERDAM

(Shell Internationale Research Maatschappij N.V.)

(Received 4 June 1960)

IN a previous publication [1] on the mechanism of the ethylene polymerization with heterogeneous Ziegler-Natta catalyst systems it was pointed out how an ethylene molecule is interposed between a Ti-ion and an alkyl group. The active center of the catalyst in the growth reaction was considered to be a Ti-ion in the surface layer of α-$TiCl_3$ of which one octahedral position is occupied by an alkyl group and another octahedral position is empty (chlorine vacancy). In this way a hole in the surface layer of the chlorine lattice is formed adjacent to the alkyl group. A monomer molecule can be incorporated in this hole and by means of a π-bond it can be attached to the alkyl-bearing Ti-ion.

Besides providing a better understanding of the driving force of the growth reaction and the possibility to explain the unique position of Ti and its neighbouring elements in producing the most active catalysts, the proposed

---

[1] P. Cossee, Tetrahedron Letters No. 17, 12 (1960).

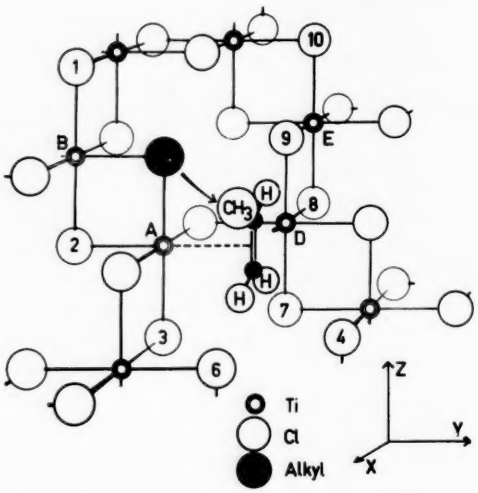


Fig. 1 Schematic drawing of part of the α-$TiCl_3$ lattice showing "active center" with monomer C_3H_6-molecule in Cl-vacancy

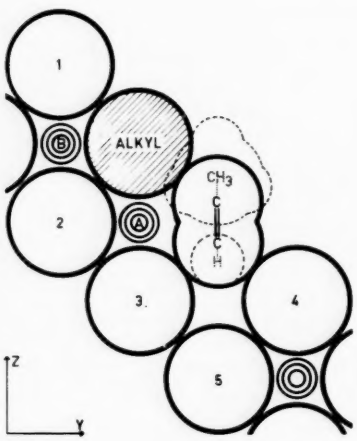


Fig. 2 ZY-Cross-section through reacting monomer

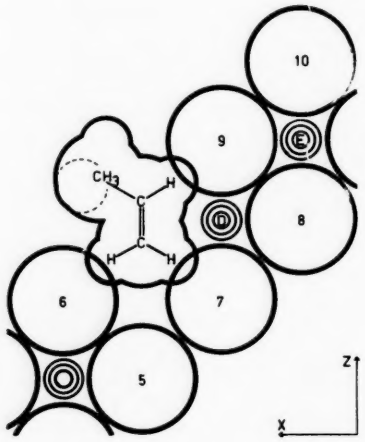


Fig. 3 XZ-Cross-section through reacting monomer

mechanism accounts for the formation of isotactic material when propylene is polymerized under the influence of α-$TiCl_3$ and Al-alkyls. It has already been pointed out by Natta [2] that the crystal structure of the solid phase is of direct importance for the stereospecificity of the reaction.

1960

In order to understand this specificity the situation at the surface of α-$TiCl_3$ must be considered in some detail. This is done in Figures 1, 2 and 3. Figure 1 is a three-dimensional schematic picture of a $TiCl_3$ lattice with the active Ti-ion carrying the alkyl group R and a molecule of C_3H_6 inserted in the chlorine vacancy in the right orientation to form a π-bond with the active Ti-ion (for a discussion of the π-bond see ref. 1). Only the relative positions of the nuclei are given. Figs. 2 and 3 are cross sections through the monomer in the Cl-vacancy parallel to the YZ and XZ planes of Fig. 1 respectively. In Figs. 2 and 3 the Van der Waals radii are drawn to scale in order to demonstrate how the monomer molecule exactly fits into the chlorine vacancy. (Corresponding Ti- and Cl-ions in the various figures are indicated by the same letter and number respectively.)

Fig. 3 demonstrates that as a consequence of the bulkiness of the methyl group in the propylene molecule the only possibility to insert the monomer into the hole is with the CH_2-group pointing into the lattice. This explains why the polymerization is exclusively a "head-to-tail" one. Figure 3 also demonstrates that, once the notion of a CH_2-group pointing into the lattice and a CH_3-group protruding out of the surface is accepted, only two different orientations of the monomer are possible: one as shown in Fig. 3, the other with the C=C double bond horizontal. In the $TiCl_3$ lattice, however, one third

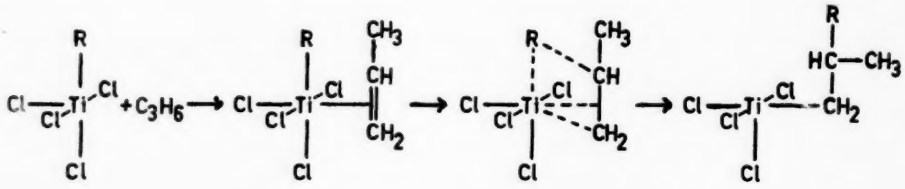
---

[2] G. Natta, J. Polymer Sci. 34, 21 (1959).

of the available octahedral metal positions in an occupied layer is empty (see Fig. 1). This means that in the orientation indicated in Fig. 3 the CH_2-group is pointing into an empty octahedral hole of the lattice, whereas in the other possible orientation this CH_2-group would be pointing towards another titanium ion.

Although it is theoretically not yet predictable which of the two non-equivalent orientations is favoured, we may assume that one of them is preferred. The orientation of each reacting monomer is thus completely fixed.

When according to the reaction scheme



described in the previous publication [1] the alkyl group R has migrated to th $C\overset{H}{\underset{CH_3}{}}$ - group of the propylene monomer, the active Ti-ion retains both an alkyl group and a vacant coordination position which have, however, mutually chang place. The alkyl group R' is one unit larger and the configuration at the ne asymmetric carbon atom (in the situation drawn in Figs. 1, 2 and 3) is such that seen from Ti into the growing chain the sequence $CH_3 \longrightarrow H \longrightarrow R$ is in a clockwise order.

If now the reaction proceeds by introduction of the next monomer molecule into the new vacant position this monomer will again prefer to point its CH_2-group towards the empty octahedral metal position. The pattern of Ti in α-$TiCl_3$ is now such that after the interposition of the monomer between Ti and growing alkyl group the sequence $CH_3 \longrightarrow H \longrightarrow R'$ is again in a clockwise

1960

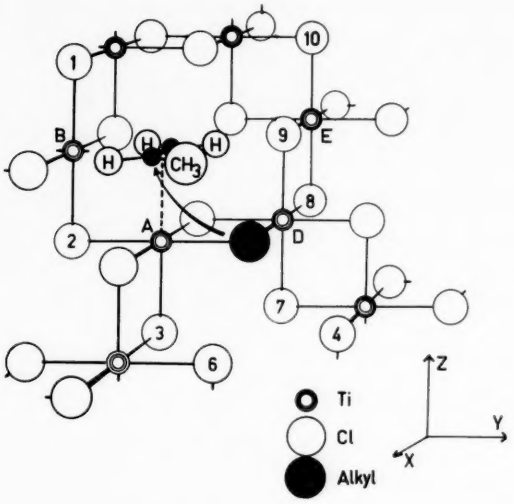


Fig. 4 Schematic drawing of the situation after migration of alkyl group R according to reaction path indicated by the arrow in Fig. 1.

The next monomer C_3H_6-molecule is placed in the new Cl-vacancy.

Reaction path of alkyl group R' is indicated.

order. This is demonstrated in Fig. 4. The proposed mechanism together with the above considerations on the $TiCl_3$-lattice thus explains the occurrence of isotactic material in a natural way. It is also clear from Figs. 2 and 3 that only α-olefins may be successfully polymerized.

It is at the same time obvious that the other carbon atom of propylene will obtain a well-defined configuration when cis- or trans-1-deutero-propylene is polymerized. This is in close agreement with Natta's [3] results in the field of di-isotactic polymers. A simple reasoning similar to that above shows that from trans-1-deutero-propylene one obtains threo-poly-1-deutero-propylene.

---

[3] G. Natta, Makromolekulare Chemie 35 (1960) 94.

Tetrahedron Letters No.17, pp. 22-26, 1960. Pergamon Press Ltd. Printed in Great Britain

HETEROCYCLE FORMATION IN THE REACTION OF α-DIAZOACETOPHENONE WITH BASES

Peter Yates and Donald G. Farnum

Department of Chemistry, Harvard University

Cambridge, Massachusetts, U.S.A.

(Received 14 June 1960)

A RECENT report from this Laboratory[1] has described an investigation of the reaction of α-diazoacetophenone with sodium methoxide in dilute solution. We now report on the reactions of α-diazoacetophenone with sodium methoxide in concentrated solution and with potassium t-butoxide, which have additional features of interest.

Addition of an equimolar amount of 7 M methanolic sodium methoxide to 5 M methanolic α-diazoacetophenone led to a violent exothermic reaction which was moderated by external cooling; after three hours the mixture was poured into aqueous sodium bicarbonate. The following products were isolated:[2] methyl benzoate, benzoic acid, (hydrogen cyanide), acetophenone, 3-benzoyl-4-phenylpyrazole (I), 3-benzoyl-4-hydroxy-5-phenylpyrazole (II), 3-benzoyl-5-hydroxy-4-phenylpyrazole (III), 5-benzoyltetrazole (IV), and a compound $C_{17}H_{11}N_5O$. Compounds I - IV were identified by direct comparison with authentic samples: the preparation of I[1,3] has been described elsewhere;

---

[1] P. Yates and B. L. Shapiro, J. Amer. Chem. Soc. 81, 212 (1959).

[2] Satisfactory elementary analyses have been obtained for all new compounds.

[3] L. I. Smith and W. B. Pings, J. Org. Chem. 2, 23 (1937).

1960

II - IV were synthesized in the following manner. Photolysis of 3-benzoyl-4-diazo-5-phenylpyrazole[4] in aqueous acetone gave II, pale yellow needles, m.p. 209-210°, λ_{max}^{Nujol} 2.97, 3.07, 6.16, 8.60, 10.28 11.05 μ. Treatment of the higher melting epimer of methyl dl-α-phenyl-β-bromo-β-benzoylpropionate[5] in boiling ethanol with hydrazine and sodium carbonate while air passed through the solution gave III, pale yellow needles, m.p. 252-254°, λ_{max}^{Nujol} 3.03, 3.18, 6.13, 6.50, 11.02 μ; two other products were obtained from this reaction: 3,5-dephenylpyrazoline-5-carboxylic acid (as its CH_2Cl_2 complex), colorless square plates, m.p. 152-155° dec., λ_{max}^{Nujol} 3.00, 4.0, 5.30, 5.90, 6.30, 6.42 μ, and 3,5-diphenyl-6-pyridazinone.[6] Oxidation of 5-benzyltetrazole[7] with chromic acid gave IV, colorless leaflets, m.p. 139-140°, $\lambda_{max}^{CH_2Cl_2}$ 2.95, 6.00, 10.85 μ.[8] The product $C_{17}H_{11}N_5O$, yellow needles with blue-green fluorescence under ultraviolet illumination, m.p. 203-204° dec., λ_{max}^{Nujol} 6.07, 6.50, 11.00 μ, is provisionally formulated as V since it is hydrolyzed in basic medium to 5-benzamido-4-benzoyl-1,2,3-triazole (VI), m.p. 266-268° dec., λ_{max}^{Nujol} 3.12, 5.97, 6.11, 6.30, 10.70 μ, identified by independent synthesis.

---

[4] P. Yates and D. G. Farnum, Chem. & Ind. 659 (1960).

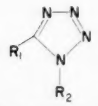
[5] E. P. Kohler and R. C. Goodwin, J. Amer. Chem. Soc. 49, 219 (1927).

[6] G. K. Almström, Ann. 400, 131 (1913).

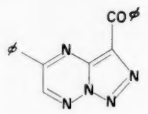
[7] W. G. Finnegan, R. A. Henry and R. Lofquist, J. Amer. Chem. Soc. 80, 3908 (1958).

[8] Since the completion of this work, an alternative synthesis of 5-benzoyltetrazole (m.p. 140-141°) has been reported: B. E. Fisher, A. J. Tomson and J. P. Horwitz, J. Org. Chem. 24, 1650 (1959).

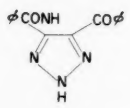
I, $R_1=\phi, R_2=H$
II, $R_1=OH, R_2=\phi$
III, $R_1=\phi, R_2=OH$



IV, $R_1=CO\phi, R_2=H$
VII, $R_1=CO\phi, R_2=CH_2CO\phi$
VIII, $R_1=H, R_2=CH_2CO\phi$



V



VI

Treatment of α-diazoacetophenone woth potassium t-butoxide in t-butyl alcohol gives a dimeric product.[9] This product, colorless needles, m.p. 114-114.5°, $\lambda_{max}^{CH_2Cl_2}$ 5.85, 5.95, 10.82 μ, λ_{max}^{EtOH} 250 mμ (log ε 4.39), has now been shown to be 5-benzoyl-1-phenacylpyrazole (VII) by its independent synthesis from IV by phenacylation; the isomeric 5-benzoyl-2-phenacyltetrazole m.p. 126-126.5°, $\lambda_{max}^{CH_2Cl_2}$ 5.85, 5.97, 10.80 μ, λ_{max}^{EtOH} 252 mμ (log ε 4.29), 272 mμ (shoulder, log ε 4.19) was also formed in this reaction. When the reaction of α-diazoacetophenone and potassium t-butoxide was carried out under heterogeneous conditions with ether as diluent, sodium benzoate precipitated; treatment of the ethereal solution with aqueous ammonium chloride gave 1-phenacyltetrazole (VIII), colorless needles, m.p. 104-104.5°, $\lambda_{max}^{CH_2Cl_2}$ 5.85, 8.15 μ. This was identified by its independent synthesis from tetrazole[10] by phenacylation; the isomeric 2-phenacyltetrazole, colorless needles, m.p. 110.5-111.5°, $\lambda_{max}^{CH_2Cl_2}$ 5.86, 8.51, 9.09 μ, was obtained as the major product from this reaction.

The following reaction scheme accomodates the formation of the several

---

[9] C.H. DePuy, unpublished results; we are greatly indebted to Professor DePuy, Iowa State University, for communicating to us the directions for this preparation and suggesting that we pursue the investigation of this reaction.

[10] R. Stollé, Ber. 62, 1118 (1929).

1960

tetrazoles and V in the reaction of α-diazoacetophenone with bases ($B^{\ominus}$):

$$\phi COCHN_2 + B^{\ominus} \rightleftharpoons [O{=}C(\phi){-}CH{=}N{=}N{-}B]^{\ominus}$$

IX

$$IX + \phi COCHN_2 \rightleftharpoons [\phi COCH{=}N{-}N(B){-}N{=}N{=}CH{-}C(\phi){=}O]^{\ominus}$$

X

$$X \rightleftharpoons \phi COCH{=}N{-}N{=}N{-}N{=}CHCO\phi + B^{\ominus}$$

XI

VII $\xleftarrow{(CH_3)_3CO^{\ominus}}$ XI $\xrightarrow{CH_3O^{\ominus}}$ IV + $\phi COCH_2OCH_3$ (XII)

$\phi CO_2^{\ominus}$ + VIII $\xleftarrow{}$ XI $\xrightarrow{CN^{\ominus}}$ V

The postulated intermediate XI may be compared with that involved in the reaction of diazonium salts with azide ion.[11] The path proposed for the formation of the chain of four nitrogen atoms is preferred to one involving removal of a proton from α-diazoacetophenone followed by attack of the anion on a second molecule of the diazoketone since it provides a rationalization for the divergence of path in the homogeneous and heterogeneous reactions with potassium t-butoxide.[12,13] Reasonable routes are available from XI and

---

[11] K. Clusius and M. Vecchi, Ann. 607, 16 (1957).

[12] It is planned to discuss this in detail in a later publication. It may be noted that VII is not converted to VIII under the conditions of the heterogeneous t-butoxide reaction, nor is it converted to IV under the conditions of the methoxide reaction.

[13] An alternative pathway for the formation of IV could involve the reduction of diazoacetophenone with sodium methoxide followed by attack of the anion of the resulting hydrazone[14] on the diazoketone. Such a route is not available, however, in the reactions with potassium t-butoxide.

[14] Cf. L. Wolff, Ann. 394, 23 (1912).

from the reaction products of XII with diazoketone to all of the other products obtained from the reaction with sodium methoxide in concentrated solution.[15]

---

[15] In dilute solution, no evidence was obtained for the formation of IV or V, and the reaction may well follow a different route after the initial terminal addition step.[1]

Tetrahedron Letters No.17, pp. 27-33, 1960. Pergamon Press Ltd. Printed in Great Britain

TOTALSYNTHETISCHE UNTERSUCHUNGEN DER STEROIDE.

TOTALSYNTHESE DES RAC. PREGNAN- UND ANDROSTANDERIVATES

W. Nagata, T. Terasawa, S. Hirai und K. Takeda

Forschungslaboratorium der Shionogi pharmazeutischen AG.

Amagasaki, Japan

(Received 26 May 1960; in revised form 23 June 1960)

Seit einigen Jahren befassten wir uns mit den Versuchen einen Weg zu finden, der nicht nur zum normalen, sondern auch zum 18-funktionierten Steroid führen könnte. Da der erstere Zweck nun erreicht wurde, berichten wir in Kürze über unsere Ergebnisse im Folgenden.

Durch zweimalige Robinson-Kondensationen mit Diäthylaminopentanon-(3)-jodmethylat, dann mit Methylvinylketon und nachfolgender Wasserabspaltung mit Natriummethylat liess sich 6-Methoxy-2-tetralon I[1, 2] analog wie die Vorschrift[3] zu Methoxyketomethyloktahydrochrysen II auf einer Ausbeute von 46% aufbauen. (II*; Smp. 140 - 141°C**, IR_{Nuj}; 1667 cm^{-1} (C=C-C=O), 1610, 1570, 1497, 881, 813 cm^{-1} (Ø-C=C-), UV: λ_{max}^{EtOH} 240 mμ, ε = 20390, 286 mμ, ε = 20150.) Reduktion von II mit Lithium und Alkohol in flüssigem Ammoniak und anschliessende saure Verseifung mit Salzsäure nach Wilds und Nelson'scher Art[4] lieferte mit guter Ausbeute (75%) ein Gemisch von dl-D-Homo-18-nor-

1 W. Salzer, Z. physiol. Chem. 274, 39 (1942); Deutsch. Patent 708,114; 714,848.

2 R. Robinson und F. Weygand, J. Chem. Soc. 1941, 386.

3 W. S. Johnson, J. Szmuszkovics, E. R. Rogier, H. I. Hadler, H. Wynberg, J. Am. Chem. Soc., 78, 6285 (1956).

4 A. L. Wilds und N. A. Nelson, J. Amer. Chem. Soc. 75, 5360 (1953).

* Die Analysenwerte sowie die optischen Daten sind nur für die wichtigen Substanzen angegeben.

** Alle Smpn. wurden auf einem Kofler-Block "Monoskop" (Hans Bock Co., Frankfurt am Rhein, Deutschland) bestimmt und korrigiert.

$\Delta^{13(17a)}$-androsten-3β-ol-17-on (III) und dessen C_8,C_{14}-Isoverbindung (IV) im Verhältnis von 3:1, das sich durch eine Al_2O_3-Chromatographie und eine fraktionierte Umkristallisation in zwei Komponenten III und IV trennen liess. (III; Smp. 183 - 185°C, IR_{Nuj}; 3400, 3310 cm^{-1} (OH), 1669, 1653, 1618 cm^{-1} (C=C-C=O), UV: λ_{max}^{EtOH} 241 mμ, ε = 17600, IV; Smp. 200 - 203°C, IR_{Nuj}; 3400 cm^{-1} (OH), 1653, 1610 cm^{-1} (C=C-C=O), UV: λ_{max}^{EtOH} 242 mμ ε = 16420). Die trans-anti-trans-anti-Konfiguration der ersteren (III) wurde aus dem Grunde erwartet, weil bei der Metall-Ammoniak Reduktion ein thermodynamisch stabiles Produkt[5] vorzüglich bildet. Erwartungsgemäss konnte dies, wie unten erwähnt, durch Überführung des letzteren zum rac. Steroidkörper XXa oder XXIa bestätigt werden.

Einwirkung von 2 Mol KCN auf III in Gegenwart von 1.75 Mol NH_4Cl resultierte in glatter Bildung eines Gemisches der zwei epimeren Additionsprodukte, 13β sowie 13α-Cyanderivat, wobei zugesetztes Ammoniumchlorid zur Hemmung der weiteren Verseifung der Cyangruppe sehr behilflich war, weil das mit dem Verlauf der Additionsreaktion gebildete Ammoniak sofort aus der Reaktionslösung vertrieben und damit deren Basizität in Minimum gehalten werden konnte. Zur Trennung beider Epimere wirkte eine Al_2O_3-Chromatographie besser nach der Ketalisierung und anschliessender Acetylierung, wonach in einer gesamten Ausbeute von 65% 13β- V und 13α-Cyanderivat VI, im Verhältnis von 5 zu 3, nämlich vorwiegend das erstere, erhalten wurden. Zum Beweis der sterischen Zuordnung beider Epimere, nämlich V für 13β- bzw, VI für 13α-Cyanverbindung, wurden folgende zwei Tatsachen festgestellt, viz. relativ stärkerer

---

5 D. H. R. Barton und C. H. Robinson, J. Chem. Soc. 1954, 3045; eine Übersicht davon, A. Z. Birch und H. Smith, Quart. Rev. 12, 17 (1958), vgl. noch W. S. Johnson, J. Amer. Chem. Soc. 75, 1498 (1953).

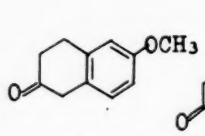
Widerstand des ersteren gegen alkalische Verseifung zum Säureamid[6] und erfolgreicher Verlauf von V, wie unten erwähnt, zum rac. Steroid. (V; Smp. 233 - 235°C, IR_{Nuj}; 2233 cm^{-1} (CN), 1730 cm^{-1} (AcO), VI; Smp. 224 - 226°C, IR_{Nuj}; 2246 cm^{-1} (CN), 1725 cm^{-1} (AcO).

Reduktion von V mit einem Überschuss an $LiAlH_4$ in Tetrahydrofuran bei Raumtemperatur verlief äusserst gut, und zwar viel besser als erwartet und lieferte auf guter Ausbeute als einiges Produkt 13β-Ketoimid, das sich, ohne sich zu isolieren, durch kurzes Kochen mit verd. NaOH in Stickstoffatmosphäre und durch nachfolgende Acetylierung direkt in eine 13β-Aldehyd-Verbindung VII ableiten liess. Durch eine Reihe Operationen, viz. Oxydierung mit CrO_3 und H_2SO_4 in Aceton[7], Entketalisierung mit verd. Salzsäure, Verseifung mit Na_2CO_3 und anschliessende Methylierung mit Diazomethan verwandelte sich VII in einen Ketocarbonsäureester, dessen Identität mit dem auf einem anderen Wege hergestellten 3β-Hydroxy-Ester VIIIa*** durch eine Mischprobe sowie direkten Verleich der IR-Spektren von sowohl dem Ester selbst, als auch von dessen Benzoat VIIIb festgestellt wurde. (VII; Smp. 172 - 179°C, IR_{Nuj}; 2742, 2680 cm^{-1} (CHO), 1726 cm^{-1} (AcO, CHO), 1708 cm^{-1} (CHO), UV: $\overset{EtOH}{max}\lambda$290 - 292 mμ ε = 35, Analyse: Gef. C: 71.00%, H: 8.92%). VII liess sich andererseits einer Huang Minlon-Reduktion unterwerfen. Die nachträgliche Entketalisierung sowie Zurückacetylierung des Reduktionsproduktes ergaben glatt dl-D-Homoandrostan-3β-ol-17-on-3-acetat IX. Zum präparativen Zweck war ein Durchlauf-Verfahren sehr geeignet, d.h., von der 13β-Cyan-Verbindung V ausgehend konnte man ohne Isolierung der Zwischen-

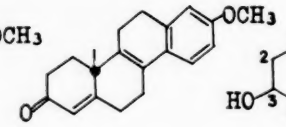
6 s. unsre Mitteilung, W. Nagata, S. Hirai, H. Itazaki, K. Takeda, beigetragen zur Zeitschrift "The Journal of Organic Chemistry".

7 A. Bowers, T. G. Halsall, E. R. H. Jones und A. J. Lemin, J. Chem. Soc. 1953, 2548.

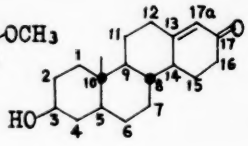
*** s. unsere bald erscheinenden Mitteilung.



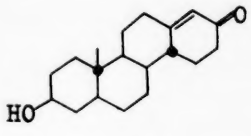
I



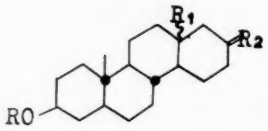
II



III



IV



V R=Ac, R_1=β-CN, R_2=

VI R=Ac, R_1=α-CN, R_2=

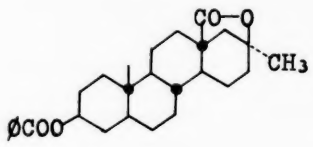
VII R=Ac, R_1=β-CHO, R_2=

VIIIa R=H, R_1=β-$COOCH_3$, R_2= =O

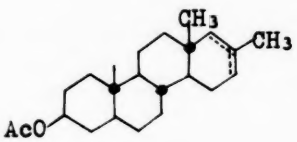
b R=ØCO-, R_1=β-$COOCH_3$, R_2= =O

IX R=Ac, R_1=β-CH_3, R_2= =O

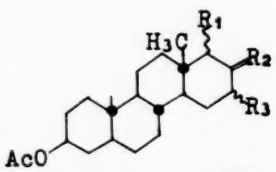
XI R=Ac, R_1=β-CH_3, R_2=



X



XII



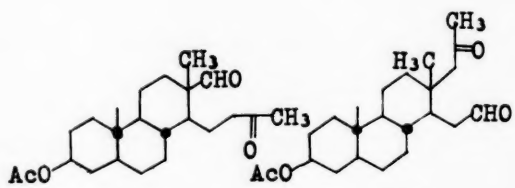
XIII R_1=β-OH, R_2= , R_3=H

XIV R_1=H, R_2= , R_3=β-OH

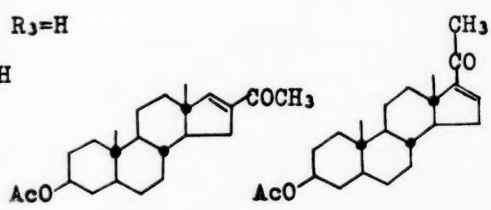
XVa dl-
b d- } R_1=α-OH, R_2= , R_3=H

XVI R_1=H, R_2= , R_3=α-OH

XVII R_1= =O, R_2= , R_3=H



XVIII XIX



XXa dl-
b d-

XXIa dl-
b d-

produkte das Endprodukt IX in einer Ausbeute von 72% bekommen. (IX; Smp. 154 - 157°/160 - 163°C (Doppeltschmp.), IR_{Nuj}; 1739 cm^{-1}, (AcO), 1711 cm^{-1} (C=O), Analyse: Gef. C: 76.30%, H: 9.77%).

Setzt man IX mit einem Überschuss an CH_3MgJ in Tetrahydrofuran um, bildet sich dann unter der sterisch selektiven Einführung des Methylrestes an 17-Carbonyl-Funktion von der α-Seite des Steroid-Moleküls ein Methylhydrin, das sich mit dem aus Lakton X*** abgeleiteten Methylhydrin XI als identisch erwies, was einen weiteren Beweis für den oben erwähnten sterischen Verlauf der Grignard-Reaktion darstellte. Auf diese Weise wurden nicht nur D-Homosteroid, sondern auch 18-oxygenierte D-Homosteroide schon in der Zwischenstufe zum ersteren sehr leicht zugänglich.

Unter trans-diaxialer Wasserabspaltung liess sich XI durch Einwirkung von $POCl_3$ in Pyridin in ein Gemisch der fast equivalenten Menge von rac. Δ^{16}-, sowie $\Delta^{17(17a)}$-D-Homoandrostanderivat (XII) verwandeln, aus dem nach OsO_4-Oxydation und anschliessender Al_2O_3-chromatographischen Trennung vier isomere cis-Diole, XIII, XIV, XVa und XVI der Reihe nach isoliert wurden. Das vorwiegende Entstehen der α-Epimere zeigte hierbei ebenfalls deutlich einen erfreulichen α-Seite-Angriff des Osmiumtetroxydes. Durch Identität des IR-Spektrums in $CHCl_3$ stellte es sich heraus, dass eines von diesen vier cis-Diolen, XVa ein Racemat des aus dem schon bekannten natürlichen D-Homoannulationsprodukt XVII[8] durch Reduktion[9] mit Aluminiumisopropoxyd abgeleiteten, optisch aktiven cis-Diol XVb darstellt. Daraus geht hervor, dass der Grundkörper der bisher abgeleiteten Verbindungen in sterischen Bezie-

---

8 J. Elphimoff-Felkin und A. Skrobak, Bull. Soc. Chim. France, 742 (1959). vgl. noch D. K. Fukushima, S. Dobriner, M. S. Heffler, T. H. Kritchevsky,

9 F. Herling und G. Roberts, J. Amer. Chem. Soc. 77, 6585 (1955). vgl. N. L. Wendler und D. Taub, J. Org. Chem. 23, 953 (1958).

hungen gleich wie der des natürlichen Steroides konstruktuiert wurde. (XIII; Smp. 240 - 242°C, XIV; Smp. 205 - 206°C, XVa; Smp. 206 - 207°C, XVb; Smp. 186 - 188°C, $[\alpha]_D^{21} = -0.7° \pm 5°$ (C = 0.582, Chf), XVI; Smp. 227 - 230°C). Zur struktuellen sowie sterischen Zuordnung der drei übrigen wurde eine Überführung von dem einen Paar Diole XIII und XVa, zu einem und demselben Ketoaldehyd XVIII einerseits und von dem anderen Paar Diole, XIV und XVI, gleicherweise zu dem anderen desselben XIX andererseits durch HJO_4-Oxydation durchgeführt, womit die vier Diole struktuell sowie räumlich klar aufeinander bezogen werden konnten. (XVIII; Smp. 118.5 - 120°C, IR_{Chf}; 2697 cm^{-1} (CHO), 1722 cm^{-1} (AcO, CHO, C=O), Analyse: Gef. C: 73.27%, H: 9.55%, XIX; Smp. 112 - 115°C, IR_{Chf}; 2711 cm^{-1} (CHO), 1725 cm^{-1} (AcO), 1714 cm^{-1}-Schulter (C=O), Analyse: Gef. C: 73.42%, H: 9.62%).

Ringschluss von XVIII und XIX zum fünf-gliedrigen D-Ring gelang glatt erst nach der Vorschrift[10] durch Kochen der Xylol-Lösung in Gegenwart von Triäthylaminacetat in einem evakuierten Gefäss und lieferte die erwünschten Endprodukte, dl-16-Acetyl-Δ^{16}-androsten-3β-ol-acetat (XXa) bzw. dl-Δ^{16}-5α-Pregnen-3β-ol-20-on-acetat (XXIa). Das IR-Spektrum von XXa in CS_2 war mit demjenigen des aus XVb nach den gleichen Reaktionsfolgen erhaltenen optisch aktiven 16-Acetyl-Δ^{16}-androstenolacetates XXb in allen Einzelheiten identisch. Die UV-Spektren der beiden waren ebenfalls miteinander identisch. Die weitere Identifizierung wurde dann bei einer Papierchromatographie beider verseiften, freien Alkohole durchgeführt, wobei beide Substanzen in einem System von Formamid-Aceton (1:2)/Toluol-Cyclohexan (1:3) denselben Rf-Wert 0.85 lieferten.

10 W. J. van der Burg, D. A. van Dorp, O. Schindler, C. M. Siegmann, S. A. Szpilfogel, Rec. trav. 77, 171 (1958).

1960

Ferner lieferte das andere synthetisierte rac. Steroid XXIa ebenfalls vollständig identisches IR- sowie UV-Spektrum mit denjenigen des in der Literatur schon bekannten, optisch aktiven Δ^{16}-5α-Pregnen-3β-ol-20-on-acetates[11] XXIb und ferner wurde die Beziehung beider Substanzen auch durch denselben Rf-Wert 0.87 ihrer verseiften freien Alkohole auf einem Papierchromatogramm in dem oben beschriebenen Lösungsmittelsystem völlig gesichert. (XXa; Smp. 163 - 165°C, IR (3.5 mg. in 0.2 cm^3 CS_2); 3050 cm^{-1} ($\geq C{=}C\leq^{H}$), 1735 cm^{-1} (AcO), 1670 cm^{-1} (C=C-C=O), 1238, 1025 cm^{-1} (OAc), 849 cm^{-1} ($\geq C{=}C\leq^{H}$), UV: λ_{max}^{EtOH} 241.5 mμ ε = 11500, Analyse: Gef. C: 76.93%, H: 9.53%, XXb; Smp. 149 - 151°C, $[\alpha]_D^{21} = -55.0° \pm 3°$ (C = 0.889 in Chf), IR (3.5 mg in 0.2 cm^3 CS_2); 3050 cm^{-1} ($\geq C{=}C\leq^{H}$), 1735 cm^{-1} (AcO), 1670 cm^{-1} (C=C-C=O), 1238, 1024 cm^{-1} (OAc), 848 cm^{-1} ($\geq C{=}C\leq^{H}$), UV: λ_{max}^{EtOH} 241.5 mμ ε = 11200, Analyse: Gef. C: 77.45%, H: 9.69%, XXIa; Smp. 167 - 169°C, IR (3.5 mg in 0.2 cm^3 CS_2); 3067 cm^{-1} ($\geq C{=}C\leq^{H}$), 1735 cm^{-1} (AcO), 1670 cm^{-1} (C=C-C=O), 1238, 1026 cm^{-1} (AcO), 819 cm^{-1} ($\geq C{=}C\leq^{H}$), UV: λ_{max}^{EtOH} 240.5 mμ, ε = 9110, Analyse: Gef. C: 77.17%, H: 9.50%, XXIb; Smp. 170 - 171°C (In Literatur; Smp. 165 - 167°C), $[\alpha]_D^{21} = +35.0 \pm 3°$ (C = 0.879 in Chf), IR (3.5 mg in 0.2 cm^3 CS_2), 3065 cm^{-1} ($\geq C{=}C\leq^{H}$), 1735 cm^{-1} (AcO), 1670 cm^{-1} (C=C-C=O), 1239, 1026 cm^{-1} (AcO), 819 cm^{-1} ($\geq C{=}C\leq^{H}$), UV: λ_{max}^{EtOH} 240.5 mμ, ε = 9230, Analyse: Gef. C: 76.87%, H: 9.49%). Ausserdem konnten XXa und XXIa aus XII durch Ozonisierung und nachfolgende Cyclisierung mit Triäthylaminacetat, wenn auch mit etwas schlechterer Ausbeute, gleich erhalten werden.

---

11 A. F. B. Cameron, R. M. Evans, J. C. Hamlet, J. S. Hunt, P. G. Jones und A. G. Long, J. Chem. Soc. 1955, 2807.

Tetrahedron Letters No.17, pp. 34-38, 1960. Pergamon Press Ltd. Printed in Great Britain

A NOVEL TYPE OF THE RING OPENING OF THE STEROIDAL 16α,17α-EPOXIDES

K. Syhora

Research Institute for Natural Drugs

U Elektry 8, Prague 9-Hloubětín, Czechoslovakia

(Received 1 July 1960)

BY oxidation of 16-methylpregna-5,16-dien-3β-ol-20-one acetate[1] with hydrogen peroxide in alkaline methanolic solution we have prepared 16β-methyl-16,17-oxidopregn-5-en-3β-ol-20-one (Ia), m.p. 192-193°, $[\alpha]_D$ -21° (Found: C, 76.58; H, 9.55. $C_{22}H_{32}O_3$ requires: C, 76.70; H, 9.36); acetate (Ib) m.p. 177-178.5°; $[\alpha]_D$ -20° (Found: C, 74.85; H, 8.66. $C_{24}H_{34}O_4$ requires: C, 74.57; H, 8.87). Reaction of the above compound (Ia) with hydrogen bromide in acetic acid - dichloromethane, unexpectedly, yielded a bromine-free isomer of Ia, for which the structure of 16-methylenepregn-5-en-3β,17α-diol-20-one (IIa) has been established; m.p. 253-255°. (Found: C, 76.40; H, 9.24. $C_{22}H_{32}O_3$ requires: C, 76.70; H, 9.36). The compound was further characterized as the 3-acetate (IIb); m.p. 204-206°; $[\alpha]_D$ 148°; I.R.-spectrum λ_{max} 1652, 1692, 1725, 3080, 3480, 3605 cm^{-1} (Found: C, 74.80; H, 8.88; H_{active}, 0.30. $C_{24}H_{34}O_4$ (one -OH) requires: C, 74.57; H, 8.87; H_{active}, 0.26); and the 3-formate (IIc); m.p. 220-222°; $[\alpha]_D$ -158.5° (Found: C, 74.28; H, 8.87. $C_{23}H_{32}O_4$ requires: C, 74.16; H, 8.66).

---

[1] A. Wettstein, Helv. Chim. Acta 27, 1803 (1944).

1960

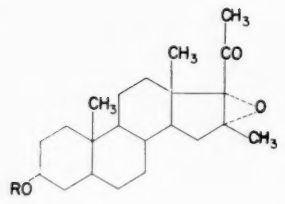
The same product (IIa) was obtained by reaction of the epoxide Ia with other acidic reagents, such as hydriodic acid in aqueous dioxane or perchloric acid in methanol. In both cases a second isomer of unidentified structure was also isolated, similar in physical properties to IIa; m.p. 275-278° (Found: C, 76.80; H, 9.52. $C_{22}H_{32}O_3$ requires: C, 76.70; H, 9.36); 3-acetate, m.p. 212-214°; $[\alpha]_D$ -166°; I.R.-spectrum λ_{max} 1695, 1725, 3490, 3605 cm^{-1}. (Found: C, 74.50; H, 8.81; H_{active}, 0.32. $C_{24}H_{34}O_4$ (one -OH) requires: C, 74.57; H, 8.87; H_{active}, 0.26). This compound contains no 16-methylene grouping. The isomerization also proceeds by the action of formic acid in Ia, the 3-formate (IIc) being obtained directly.

The structure II was proved by reduction of the 3-acetate (IIb) with sodium borohydride to the 17,20-diol, followed, without isolation, by oxidative cleavage with periodic acid to the known[2] 16-methylene-androst-5-en-3β-ol-17-one acetate (V) and acetaldehyde (identified as the dimedone derivative). The presence of the 16-methylene grouping in II was also verified by the ozonization of compounds IIb, IIe and V and identification of the formaldehyde formed by means of the modified Schiff reagent.

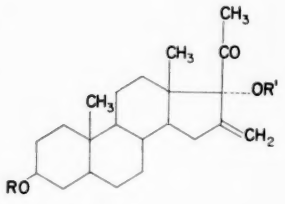
The generality of the above isomerization was demonstrated by a similar reaction sequence in the 5α-pregnane series. Addition of diazomethane to 5α-pregn-16-en-3β-ol-20-one acetate afforded the corresponding pyrazoline, m.p. 150-151° (decomp.) (Found: C, 72.12; H, 9.20. $C_{24}H_{36}N_2O_3$ requires: C, 71.96; H, 9.06), which on thermal decomposition at 150-170° gave 16-methyl-5α-pregn-16-en-3β-ol-20-one acetate; m.p. 169-170° (Found: C, 77.08; H, 9.72. $C_{24}H_{36}O_3$ requires: C, 77.37; H, 9.74). On oxidation with hydrogen in alkaline

---

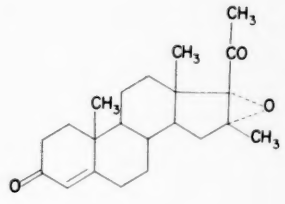
[2] P. L. Julian, E. W. Meyer and H. C. Printy, J. Amer. Chem. Soc. 70, 3872 (1948).



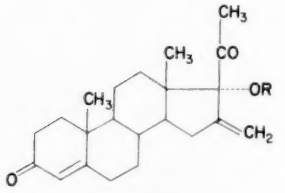
I a Δ^5; R=H—
b Δ^5; R=Ac—
c 5α; R=H—



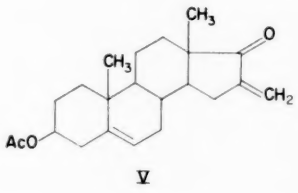
II a Δ^5; R=R'=H
b Δ^5; R=Ac—; R'=H—
c Δ^5; R=HCO—; R'=H—
d 5α; R=R'=H—
e 5α; R=Ac—; R'=H—
f Δ^5; R=HCO—; R'=Ac—



III



IV a R=H—
b R=Ac—



V

methanolic solution, the latter compound gave 16β-methyl-16,17-oxido-5α-pregnan-3β-ol-20-one (Ic); m.p. 186-188°; $[\alpha]_D$ +54.5°. (Found: C, 76.01; H, 9.62. $C_{22}H_{34}O_3$ requires: C, 76.26; H, 9.89). The same product was obtained by hydrogenation of Ia on $Pd/CaCO_3$ in methanol. The isomerization of Ic with hydrogen bromide in acetic acid - dichlormethane afforded 16-methylene-5α-pregnan-3β,17α-diol-20-one (IId), m.p. 236-239°; (Found: C, 76.31; H, 9.83. $C_{22}H_{34}O_3$ requires: C, 76.26; H, 9.89); 3-acetate (IIe);

m.p. 180-182°; $[\alpha]_D$ -88°. (Found: C, 73.97; H, 9.08. $C_{24}H_{36}O_4$ requires: C, 74.19; H, 9.34).

A similar isomerization was brought about by the action of hydriodic acid on a dioxan solution of 16β-methyl-16,17-oxidopregn-4-en-3,20-dione (III); m.p. 165° (Found: C, 77.01; H, 9.02. $C_{22}H_{30}O_3$ requires: C, 77.15; H, 8.83), obtained by Oppenauer oxidation of Ia. The product of the isomerization reaction - 16-methylenepregn-4-en-17α-ol-3,20-dione (IVa); m.p. 218-221°; $[\alpha]_D$ -3.8°; E^{EtOH}_{max} 240 mμ (log ε 4.24) (Found: C, 77.12; H, 8.91. $C_{22}H_{30}O_3$ requires: C, 77.15; H, 8.83) was identical with the product of a mild hydrolysis (potassium hydrogen carbonate) of 17α-acetoxy-16-methylenepregn-4-en-3,20-dione (IVb)*; m.p. 231-233°; $[\alpha]_D$ -56°; E^{EtOH}_{max} 240 mμ (log ε 4.41) (Found: C, 74.75; H, 8.22. $C_{24}H_{32}O_4$ requires: C, 74.97; H, 8.39). This in turn was obtained from IIc by acetylation of the 17α-hydroxyl group with acetic anhydride and toluene-p-sulphonic acid to the corresponding 3-formate 17-acetate (IIf); m.p. 178-180°; $[\alpha]_D$ -169.5° (Found: C, 74.25; H, 8.12. $C_{25}H_{34}O_5$ requires: C, 72.43; H, 8.27), followed by Oppenauer oxidation of the latter compound.

The unusual course of the epoxide ring cleavage may be ascribed mainly to the ditertiary character of the epoxide ring in conjunction with the steric conditions on the highly substituted and relatively rigid cyclopentanone system. The usual attack of the halogen anion from the "front" side is in this case hindered by the 16β-methyl group and thus the structure formed by

---

* A paper which, judging by the title, also deals with the preparation of IVb, has recently been submitted for publication[3], though no details are yet known.

[3] D. N. Kirk, V. Petrow, M. Stansfield and D. M. Williamson, J. Chem. Soc. No. 4, xi (1960).

fission of the $C_{(16)}$-O linkage in the protonated epoxide is stabilized by elimination of the hydrogen from the neighbouring carbon atom. This reaction course formally recalls formation of the $\Delta^{8(14)}$-11β-ol-system by the action of strong acids on the 9β,11β-epoxide ring, stabilization in this case, however, proceeding through transannular hydrogen transfer.[4]

This work is intended to be published in full in the Coll. Czech. Chem. Comm.

The author is indebted to Dr. Z. Čekan, Director of the Institute, and to Dr. J. Trojanek for fruitful discussion; to R. Mazáč for technical assistance.

---

[4] N. L. Wendler, R. P. Graber, C. S. Snoddy, Jr. and F. W. Bollinger, J. Amer. Chem. Soc. 79, 4476 (1957); J. Fried and E. F. Sabo, Ibid. 79, 1130 (1957).

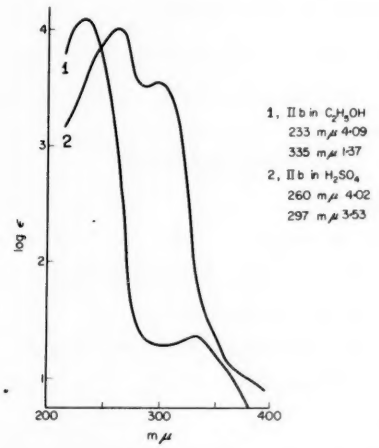
Tetrahedron Letters No.17, p. 39, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

ERRATUM

H. BUDZIKIEWICZ: Bemerkungen zu der Arbeit von S. M. Bloom: "An acid stable cyclohexadienon", Tetrahedron Letters No. 7, 12 - 16 (1960).

The author has pointed out that an incorrect U.V.-spectrum was submitted and published with the above article. The correct spectrum is reproduced below.



19

Tetrahedron Letters No. 18, pp. 1-3, 1960. Pergamon Press Ltd. Printed in Great Britain

THE EFFECT OF THE LEAVING GROUP ON ORIENTATION IN E2 ELIMINATION REACTIONS[1]

William H. Saunders Jr., Susan R. Fahrenholtz and John P. Lowe

Department of Chemistry, University of Rochester,

Rochester, New York

(Received 8 June 1960)

The widely-accepted belief that the Hofmann rule is the consequence of polar effects[2] has recently been challenged by Brown,[3] who points out that the proportion of the less-alkylated olefin increases as the steric requirements of the leaving group increase. In most of his examples, an explanation based on the ease of heterolysis of the C-X bond and the inductive effect of X predicts the same trend. When X is halogen the predicted trends for the steric vs. the polar explanations are not parallel, but in several instances Brown[3] reports no sig-

---

[1] This work was supported in part by the National Science Foundation.

[2] (a) M. L. Dhar, E. D. Hughes, C. K. Ingold, A. M. M. Mandour, G. A. Maw and L. I. Woolf, J. Chem. Soc. 2093 (1948);

(b) W. Hanhart and C. K. Ingold, ibid. 997 (1927).

[3] (a) H. C. Brown and O. H. Wheeler, J. Amer. Chem. Soc. 78, 2199 (1956);

(b) H. C. Brown and I. Moritani, ibid. 78, 2203 (1956);

(c) C. H. Schramm, Science 112, 367 (1950).

nificant effect on olefin proportions of changing the halogen.

We have now studied eliminations from 2-pentyl and 2-methyl-2-butyl halides using gas chromatography (a technique not available at the time of Brown's work) to determine product compositions. Separation of 1-olefin from 2-olefin in both series was effected by di-n-decyl phthalate as stationary phase. Eliminations were run at reflux in absolute ethanol with 1.0-1.5 M halide and 1.0-3.3 M potassium or sodium ethoxide.

With 2-methyl-2-butyl, the proportion of 2-methyl-1-butene was 43.1% from the chloride and 33.5%[4] from the bromide. With 2-pentyl, the proportion of 1-pentene ran: Chloride, 36.8%; bromide, 24.7%; and iodide, 19.6%.[5] All percentages are averages from three or more runs and average deviations were less than 2%. Purity of starting materials was established by gas chromatography and infrared spectra. We determined that solvolytic (E1) eliminations made negligible contributions in all reactions studied.

---

[4] H. C. Brown, I. Moritani and M. Nakagawa, J. Amer. Chem. Soc. 78, 2191 (1956) report 30% 1-olefin from the bromide.

[5] Ref. 3a reports 31% 1-pentene from the bromide and 30% 1-pentene from the iodide. We have no good explanation of the discrepancies between these infrared analyses and our gas-chromatographic analyses.

1960

Clearly, the results are in the wrong order for the steric explanation. The order of increasing ease of heterolysis of the C-X bond is Cl < Br < I, however, so one might expect double-bond character in the transition state to increase in the same order. Thus the tendency for the more stable olefin to predominate should be greatest for the iodide and least for the chloride, in agreement with our results. The change in inductive effect with changing halogen is probably of minor importance, but also predicts the observed order.

Our results do not, of course, prove that steric effects are unimportant with bulky leaving groups such as trialkylammonium. Obviously further work is necessary, but until more definitive evidence is available it seems unwise to assume that the steric requirements of the leaving group have any important effect on the olefin proportions in E2 eliminations.

Tetrahedron Letters No. 18, pp. 4-9, 1960. Pergamon Press Ltd. Printed in Great Britain

EFFETS CONFORMATIONNELS SUR L'EQUILIBRE CIS-TRANS D'α-HYDRINDANONES

J. F. Biellmann, D. Francetić et G. Ourisson

Institut de Chimie, 2, rue Goethe, Strasbourg

(Received 5 July 1960)

NOUS avons annoncé précédemment la préparation de deux types d'α-hydrindanones trans - d'une part dans le cycle D de dérivés du dammarane,[1] d'autre part dans le cycle A-nor triterpènes et de 4,4-diméthyl stéroïdes.[2]

La contraction de cycle rétropinacolique utilisée dans ce dernier cas a été étendue à la série 4,4-diméthyl 19-nor stéroïde, comme le montre le Tableau 1. L'action de PCl_5 sur le 3β-hydroxy 17β-acétoxy 4,4-diméthyl 19-nor (5α) androstane (I)[3] donne, comme on pouvait le prévoir,[4] un mélange de dérivés A-nor isopropylidénique (II) et A-nor isopropénylique (III), séparables par chromatographie et ozonisables individuellement pour donner les cétones de coupure correspondantes (IVt) et (V). La cétone trans (IVt) est ici isolable sans précautions spéciales, et isomérisable en milieu acide ou alcalin en son épimère 5β (IVc).

---

[1] J. F. Biellmann, P. Crabbé et G. Ourisson, Tetrahedron 3, 303 (1958).

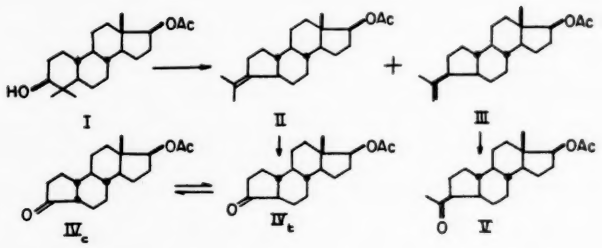
[2] J. F. Biellman et G. Ourisson, Bull. Soc. Chim. Fr. 348 (1960).

[3] Obtenu à partir de la 3-cétone 5-éthylénique correspondante: A. Bowers et H. J. Ringold, J. Amer. Chem. Soc. 81, 424 (1959).

[4] cf. J. F. Biellmann, Thèse d'Ingénieur-Docteur, Strasbourg (1959).

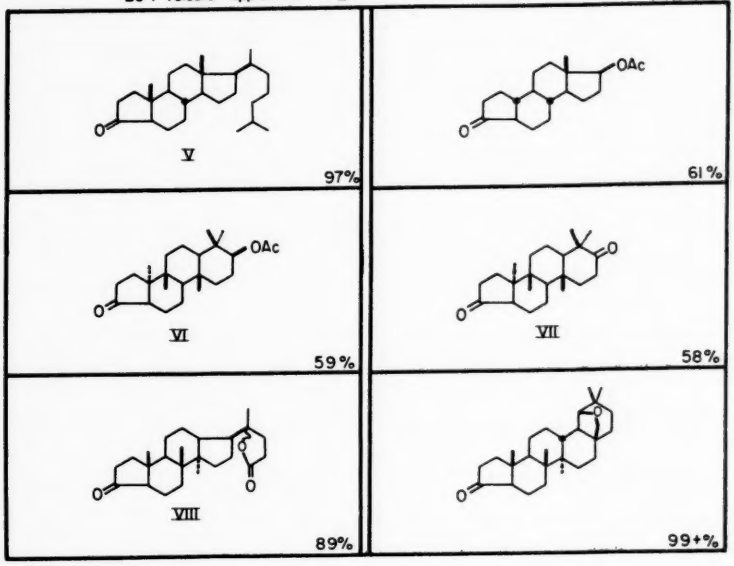
1960

Tableau 1



I: F=187°; $[\alpha]_D$ +5° (Chf)
II; F=158°; $[\alpha]_D$ −20° (Di)
III; F=130°; $[\alpha]_D$ −24° (Di)
IV: t −F=154°; $[\alpha]_{600}$ −93; $[\alpha]_{310}$ −3400; $[\alpha]_{270}$ +3780; $[\alpha]_{260}$ +3250° (MeOH)
c −F=143°; $[\alpha]_{600}$ +170; $[\alpha]_{315}$ +2000; $[\alpha]_{280}$ −1013° (MeOH)
F=142°, $[\alpha]_{600}$ +60; $[\alpha]_{302}$ +799, $[\alpha]_{270}$ −430° (MeOH)

Tableau 2. Pourcentages de forme cis à l'équilibre, dans l'acide acétique à 25°. Valeurs approchées à ± 1% env., sauf pour IV (± 2%).



L'effet Cotton très intense, et de signe opposé, des cétones cis et trans, permet une étude aisée et précise de leur isomérisation réciproque. Dans tous les cas, nous avons mesuré les courbes de dispersion rotatoire des isomères purs, dans l'acide acétique, avant et après addition d'une petite quantité, constante, d'acide chlorhydrique. L'équilibre est atteint, d'un côté et de l'autre, instantanément dans tous les cas, sauf dans la série 19-nor stéroïde, où un délai de plusieurs heures est nécessaire ce qui limite la précision des mesures par suite de l'intervention probable de réactions secondaires.

Le Tableau 2 résume les résultats obtenus, que nous pensons pouvoir interpréter par l'intervention de plusieurs effets conformationnels à courte, moyenne, et grande distance. La comparaison des cétones 19-nor A-nor stéroïdes (IVc et IVt) avec les cétones A-nor stéroïdes (Vc et Vt) traduit l'effet du groupe angulaire en C-10. Le remplacement d'un hydrogène par un méthyle doit déstabliser relativement la forme trans, dans laquelle la liaison C_3-C_5 et la liaison C_{10}-C_{19} (au lieu de C_{10}-H) sont cis-gauches (Fig. 1). L'effet prévu est observé.

La comparaison, avec les cétones A-nor stéroïdes (V), des 17-cétones dammaraniques VI et VII (à peu près équivalentes à des 9α-méthyl A-nor stéroïdes, non étudiés) traduit l'effet d'une interaction 1-3 directe. Le remplacement d'un hydrogène par un méthyle (axial) doit déstabiliser relativement la forme cis, dans laquelle le groupe carbonyle est directement en interférence avec ce groupe axial (Fig. 2). L'effet prévu est observé.

La comparaison des cétones A-nor dammaraniques (VIII) avec les cétones A-nor stéroïdes (IV) traduit l'effet de boutoir du groupe méthyle en C-8

1960

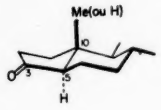
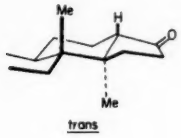


FIG. 1



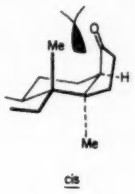


FIG. 2

FIG. 3

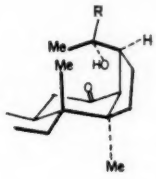


FIG. 4

sur C-19, et l'effet réflexe concomitant.[5] Dans la forme cis, la déformation imposée au squelette sur la face β amène une augmentation réflexe du caractère axial de C-3 (Fig. 3); la déstabilisation relative de cette forme cis, prévue d'après ces considérations, est observée.

Cet effet conformationnel à moyenne distance est cependant contrebalancé en série triterpénique pentacyclique par un effet conformationnel à grande distance[6] qui était imprévisible. La cis-hydrindanone dérivant de l'allobétuline (IXc) est en effet pratiquement seule présente dans le mélange équilibré. Nous attribuons la différence des pourcentages à l'équilibre des cétones (VIIIc) et (IXc) à la différence de taille de leur cycle D. Cette

---

[5] C. Sandris et G. Ourisson, Bull. Soc. Chim. Fr. 1524 (1958).

[6] D. H. R. Barton, F. McCapra, P. J. May et F. Thudium, J. Chem. Soc. 1297 (1960); et publications antérieures.

hypothèse sera, nous l'espérons, vérifiée p. ex. sur des dérivés A-nor D-homo stéroïdes.

Par contre, l'identité des résultats obtenus dans les deux séries de 17-cétones dammaraniques VI et VII démontre, dans ce cas, l'absence d'effet conformationnel à grande distance.

Enfin, un dernier exemple démontre l'influence, prévisible, de facteurs structuraux particuliers. Le 3,12-dioxo 20 ξ_2-hydroxy dammarane, 13βH, C/D trans, dérivé du bétulafoliènetriol ("20-Hydroxyfoliandion-3,12"),[7] a une dispersion rotatoire, positive, presque inchangée dans un milieu équilibrant. Dans ce cas, la cétone 13α, cis, est manifestement déstabilisée complètement par suite de l'interaction qu'elle présenterait entre C-20, très volumineux, et le méthyle angulaire en C-8 (Fig. 4). La différence entre ce cas et celui des 17-cétones dammaraniques (VI) et (VII) traduit, au moins en grande partie, la différence de taille entre les groupements liés à C-17, trigonal dans un cas, tétraédrique et très lourdement substitué dans l'autre. Ce bloquage de la forme trans est évidemment apparenté au bloquage de conformation maintenant classique par le groupe t-butyle.

Une étude menée indépendamment par Allinger et al.[8] recoupe une partie de nos résultats; nous reprendrons dans la publication définitive la discussion quantitative des effets observés.

Nous remercions MM. Allinger et Djerassi de nous avoir communiqué à l'avance leur manuscrit.

---

[7] F. G. Fischer et N. Seiler, Ann. Chem. 626, 185 (1959). Nous remercions le Prof. F. G. Fischer pour un échantillon de cette cétone.

[8] N. L. Allinger, R. B. Hermann et C. Djerassi, J. Org. Chem. 25, 922 (1960).

Nous remercions pour des allocations la Direction du CNRS (JFB) et l'Université de Strasboug (DF). La réalisation de ce travail a été aidée par une subvention de N.V. Organon (OSS), qui nous a aussi généreusement fourni les matières premières stéroïdes.

1960

Tetrahedron Letters No. 18, pp. 10-16, 1960. Pergamon Press Ltd. Printed in Great Britain

IONIZATION AND DISSOCIATION EQUILIBRIA OF SOME TRIPHENYLCHLOROMETHANE DERIVATIVES IN NITROBENZENE AT 25°

E. Price and N. N. Lichtin

Department of Chemistry

Boston University, Boston, Mass.

(Received 17 June 1960; in revised form 6 July 1960)

EVANS and his associates have reported numerous data on ionization equilibria of derivatives of triphenylchloromethane in solution in nitroalkanes,[1] nitroaromatics,[2] chlorinated ethanes[3] and acetic and formic acids[4] based on spectrophotometric measurements. They conclude that the only equilibrium involved in many of these solvents is between the covalently bonded molecules and associated ion pairs. Thus, with nitro compounds (dielectric constant, D, in the range 24-35) as solvents, they report that dissociation to free ions is not detectable, a result which has been questioned[5] because

---

[1] A. Bentley, A. G. Evans and J. Halpern, Trans. Faraday Soc. 47, 711 (1951); A. Bentley and A. G. Evans, J. Chem. Soc. 3468 (1952); A. G. Evans, J. A. G. Jones and G. O. Osborne, Trans. Faraday Soc. 50, 16 (1954); A. G. Evans, J. A. G. Jones and G. O. Osborne, Ibid. 470 (1954); A. G. Evans, J. A. G. Jones and G. O. Osborne, J. Chem. Soc. 3803 (1954).

[2] A. G. Evans, A. Price and J. H. Thomas, Trans. Faraday Soc. 50, 568 (1954).

[3] A. G. Evans, A. Price and J. H. Thomas, Trans. Faraday Soc. 52, 332 (1956).

[4] A. G. Evans, A. Price and J. H. Thomas, Trans. Faraday Soc. 51, 481 (1955).

[5] N.N. Lichtin and H.P. Leftin, J. Phys. Chem. 60, 164 (1956).

conductivity data demonstrate extensive dissociation of many wholly ionic solutes in solution in nitromethane[6] and nitrobenzene[7] at concentrations cited by these workers. Other data[8] for solutions of triphenylchloromethane in nitromethane cast doubt on Evans' results in this solvent. Evans et al.[4] report that in the solvent formic acid (D_{16} = 58.5) at 21.5° triphenyl carbonium chloride ion pair is detectably dissociated but the "extent was too small for estimation". Electrostatic ionic association in a medium of such high dielectric constant would be expected to be negligible.[9]

Evans and his coworkers report dissociation of ion pairs in several solvents of lower dielectric constant, however. Thus, the dissociation constant of the ion pair tri-p-tolycarbonium chloride in acetic acid solution at 21.5° (D_{20}=6.15), was found[4] to be 6 x 10^{-8} mole fraction. The value of this constant in several chlorinated ethanes in which $3.6 \ll D_{20} \ll 11.9$ fell[3] in the range 3 x 10^{-7} to 3 x 10^{-6} mole fraction.

Because of its relatively high dielectric constant (D_{25}=34.5) and the absence of reaction between this solvent and solutes of the type discussed here, we undertook to reinvestigate the ionization and dissociation behavior of triphenylchloromethane and some of its derivatives in nitrobenzene solution at 25°. In this study, the final degassing and distillation of

---

[6] C. P. Wright, D. M. Murray-Rust and H. Hartley, J. Chem. Soc. 199 (1931); R. C. Miller and R. M. Fuoss, J. Amer. Chem. Soc. 75, 3076 (1953).

[7] C. R. Witschonke and C. A. Kraus, J. Amer. Chem. Soc. 69, 2472 (1947).

[8] cf. B. B. Smith and J. E. Leffler, J. Amer. Chem. Soc. 77, 1700 (1955); Y. Pocker, J. Chem. Soc. 240 (1958), for evidence of the instability of solutions of trityl chloride in nitromethane.

[9] The significance of this result is somewhat obscured by the fact that formic acid is known to reduce trityl chloride fairly rapidly at 100°C. cf. S.T. Bowden and T.F. Watkins, J. Chem. Soc. 1333 (1940).

solvent and the preparation of solutions were carried out on the high vacuum line under an atmosphere of solvent. Optical density and electrical conductivity were determined on the same solution in cells which had been sealed under vacuum. Free ion concentrations were calculated from conductivity data while the sums of free and associated ion concentrations were calculated from optical densities. It was found that, in solutions up to 1×10^{-5} M in carbonium ion, the concentration of free ions is indistinguishable from the total ionic concentration. This result conflicts with that of Evans et al.[2] who report only paired ions in 10^{-6} to 2×10^{-5} M solutions of triaryl carbonium ions in nitrobenzene.

No significant spectrophotometric data could be obtained with solutions of unsubstituted triphenylchloromethane because nitrobenzene absorbs strongly at the wave length of the carbonium ion maximum. Conductance data indicate a very low degree of dissociation.

With 0.002 to 0.015 M mono-p-tolyldiphenylchloromethane the concentration of carbonium ion was too small to measure accurately. The absorbancy, A_s[10], of a 0.015 M solution at λ_{max} (462 mu) was 0.04 initially and tripled in 24 hr. Evans et al.[2] report $A_s = 1.21$ for a 0.088 M solution of this compound at 16.5° in what appears to have been a 1 cm cell and that ΔH° of ionization is + 0.5 kcal mole^{-1}.

Solutions of tri-p-t-butylphenylchloromethane were investigated in an attempt to obtain solutions of higher conductivity and optical density. Work with this solute was limited because of its extremely slow rate of

---

[10] All A_s values are in 1 cm cells and were determined against a solvent blank in a double beam instrument. The solvent cell was always charged on the vacuum line at the time when the solutions were prepared.

dissolution. The equivalent conductance, Λ,[11] of a 6.2×10^{-4} M solution was 0.12 mho cm^2 $mole^{-1}$ and A_s at λ_{max} (469 mμ in nitrobenzene) was 0.204. These data yield crude estimates of the concentrations of free ions and total ions. Thus, if Λ^{o}[7] and a_m[12] are assumed to be 30 and 8.31×10^4 respectively, the free ion and total ion concentrations are both 2.5×10^{-6} M. Analogous results were obtained with a 2.3×10^{-4} M solution.

More conclusive results were obtained with solutions of tri-p-anisylchloromethane. Conductivity data were obtained in the concentration range 4.55×10^{-5} to 8.18×10^{-4} M[13] where A_s was too large to measure accurately. The limiting equivalent conductance, Λ^{o}, and the equilibrium constant, K_{exp},[14] were found by Shedlovsky's procedure[15] to be 31 ± 3 mho cm^2 $mole^{-1}$ and $(4.2 \pm 1) \times 10^{-5}$ mole l^{-1}, respectively.

Spectrophotometric measurements distinguish between free ions and ion

---

[11] All conductivity data are corrected for solvent conductivity.

[12] N. C. Deno, J. J. Jaruzelski and A. Schriesheim, J. Org. Chem. 19, 155 (1955).

[13] The conductivities of these solutions did not increase over a period of 24 hr.

[14]

$$K_{exp} = \frac{[R^+][Cl^-]}{[RCl]+\overbrace{[R^+Cl^-]}} = \frac{K_1K_2}{1 + K_1}$$

$$K_1 = \frac{\overbrace{[R^+Cl^-]}}{[RCl]} \qquad K_2 = \frac{[R^+][Cl^-]}{\overbrace{[R^+Cl^-]}}$$

The terms in brackets are activities.

[15] T. Shedlovsky, J. Frank. Inst. 225, 739 (1938).

pairs on the one hand, and covalent molecules on the other,[16,17,18] so that, for these solutions, $A_s = a_m b [(R^+) + \overbrace{(R^+Cl^-)}]$.[19] The value of a_m for trianisyl carbonium ion at λ_{max} in nitrobenzene was found by adding an excess of mercuric chloride to solutions of the organic halide[20] to be $(10.4 \pm 0.8) \times 10^4$ at 498 mμ. This procedure was employed because a_m for sulfuric acid solutions of this chloride or its carbinol was lower[21] than that reported in the literature[12] and the solutions were unstable. Solutions of tri-p-anisylchloromethane adhered to Beer's Law over the concentration range 1.52×10^{-6} to 11.8×10^{-6} M in the presence of either 1.6 or 5 moles of $HgCl_2$ per mole of organic solute.

The measurements summarized in Table 1 were made at such low concentrations that the equation $(R^+) = 10^3 k/\Lambda^\circ$, where k is the specific conductance of the solute, can be used to estimate the concentration of free ions, (R^+).

From the data of Witschonke and Kraus[7] it can be estimated that K_2[14] is of the order of 10^{-2} mole l^{-1} for these solutes in nitrobenzene. At the very low solute concentrations of Table 1 ion pairing would, thus, be negligible even if ionization were complete. The data of Table 1 are in

---

16 L. P. Hammett, Physical Organic Chemistry p. 50. McGraw-Hill, New York (1940).

17 G. N. Lewis, T. T. Magel and D. Lipkin, J. Amer. Chem. Soc. 64, 1774 (1942).

18 A. G. Evans, I. H. McEwan, A. Price and J. H. Thomas, J. Chem. Soc. 3098 (1955).

19 $A_s = \log_{10} (Io/I)$; $a_m = A_s/bc$, where b = cell path length in cm; c = concentration in moles l^{-1}.

20 cf. J. L. Cotter and A. G. Evans, J. Chem. Soc. 2988 (1959).

21 With this value, $a_m = 7.43 \times 10^4$, the concentrations of carbonium ion appeared to be greater than the stoichiometric concentrations or organic chloride.

agreement with this conclusion. Differences between free ion concentration measured by electrical conductivity and total ion concentration measured by spectrophotometry are within experimental error, in direct disagreement with Evans et al.[2]

An interesting comparison between the "ionizing power" of nitrobenzene (D_{25} = 34.5) and SO_2 (D_0 = 15.4) can be made. Assuming that $K_2 = 10^{-2}$ in nitrobenzene, K_1[14] of tri-p-anisylchloromethane is about 4×10^{-3}. The value of K_1 for this solute in liquid SO_2 at 0°, calculated from ρ = -4.41[5], $K_1 = 1.5 \times 10^{-2}$ for triphenylchloromethane[22] and σ^+ = -0.764 for p-methoxy,[23]

TABLE 1

Free and Total Ion Concentrations in Very Dilute Solutions of tri-p-Anisylchloromethane in Nitrobenzene at 25°

$10^5 C_s$ [a] (mole l^{-1})	$10^5(R^+)$ [b] (mole l^{-1})	$10^5[(R^+)+\widetilde{(R^+Cl)}]$ [b] (mole l^{-1})
0.37	0.22 ± 0.02	0.24 ± 0.02
0.67	0.52 ± 0.05	0.66 ± 0.05
0.71	0.53 ± 0.05	0.59 ± 0.05
1.73	0.98 ± 0.10	1.14 ± 0.10

a Stoichiometric concentration of solute.

b Uncertainties based on uncertainty in Λ° and a_s, respectively.

[22] N. N. Lichtin and M. J. Vignale, J. Amer. Chem. Soc. 79, 579 (1957).

[23] H. C. Brown and Y. Okamoto, J. Amer. Chem. Soc. 79, 1913 (1957).

is $2 \times 10^{+8}$. The 5×10^{10} fold difference is a measure of the immensely greater "ionizing power" of SO_2, a property which is not related even approximately to its dielectric constant. The relative abilities of nitrobenzene and liquid SO_2 to promote the dissociation of ion pairs are related in a qualitative fashion to their dielectric constant, however.[7,24] We wish to emphasize the necessity of distinguishing carefully between these two functions of the solvent in the elucidation of chemical mechanisms.

We wish to express our appreciation for support of this work by the National Science Foundation.

---

[24] cf. N. N. Lichtin and H. P. Leftin, J. Phys. Chem. 60, 160 (1956); N. N. Lichtin and P. Pappas, Trans. N.Y. Acad. Sci. 20, 143 (1957).

Tetrahedron Letters No. 18, pp. 17-23, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

REDUCTION OF CARBON DIOXIDE IN AQUEOUS SOLUTIONS UNDER THE INFLUENCE OF RADIATION

N. Getoff, G. Scholes and J. Weiss

Dept. of Chemistry, University of Durham, Kings College,

Newcastle upon Tyne

(Received 7 July 1960)

^{60}Co-γ-Radiation

GARRISON et al.[1] have previously reported that carbon dioxide can be reduced to formic acid on irradiation of air-free CO_2 solutions with 40 MeV He ions, and in the presence of ferrous ions, small quantities of formaldehyde were also detected.

We have investigated in some detail the effect of ^{60}Co-γ-rays on CO_2 in aqueous solutions under various conditions. It has been found that this can lead initially to the formation of formaldehyde, acetaldehyde and formic acid, whilst there are indications that oxalic and glycol are also formed, particularly after higher doses or radiation.

The yields of aldehyde and formic acid and their dependence on radiation dose and on pH have been determined. Solutions were made up in water which had been distilled at least three times. Pure carbon dioxide was prepared from sodium carbonate (A.R.) and sulphuric acid (A.R. and was

---

[1] W. M. Garrison, D. C. Morrison, J. G. Hamilton, A. A. Benson and M. Calvin, Science 114, 416 (1951).

subsequently purified by several sublimations.

Experiments were carried out over a considerable pH range: to adjust the pH, sulphuric acid, sodium bicarbonate and sodium carbonate were used. Solutions were first evacuated and then saturated with carbon dioxide (1 atm).

The aldehydes formed were formaldehyde and acetaldehyde as shown by paper chromatography.[2] The total aldehydes were estimated as 2:4 dinitrophenylhydrazone[3] and evaluated as if only formaldehyde was present. Some typical yield-dose plots for the production of aldehydes at various pH's are shown in Fig. 1. It is interesting to note that at low pH's and in the

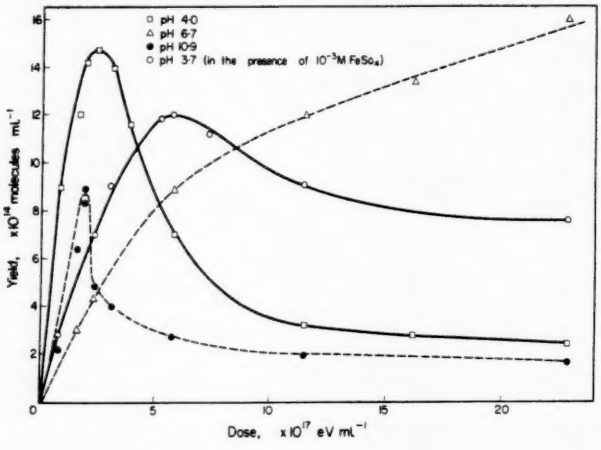


FIG. 1.

Yields of aldehydes from the irradiation (^{60}Co-γ-rays) of aqueous solution of CO_2 at different pH values.

more alkaline solutions the aldehyde yields go through a maximum after a fairly low radiation dose (1 to 6 x 10^{17} eV ml^{-1}). In the intermediate pH

---

[2] J. Gasperic and M. Vecera, Coll. Czech. Chem. Comm. 22, 1426 (1957).

[3] G. R. A. Johnson and G. Scholes, Analyt. Chem. 79, 217 (1954).

1960

range, on the other hand, no such maxima were observed. The nature of the yield-dose plots as well as the limited accuracy of the aldehyde determination at the lowest radiation doses makes it rather difficult to assess with any great certainty the values of the initial yields. It is obvious, however, that the formation of aldehyde is quite an important radiation-induced reaction; for example for the initial yield at pH 4.0 a G(HCHO) = 0.85 (G = molecule/100 eV) was found.

The presence of ferrous ions influence the yield of aldehyde, presumably by protecting the aldehyde from back reactions with the radiation-produced active species. This would account for the fact that Garrison et al.[1] could not tetect formaldehyde in solutions irradiated in the absence of ferrous salts.

Some data for the extent of formation of formic acid on irradiation are given in Table 1. The yields of formic acid, which were determined by the

TABLE 1

Irradiation of Aqueous Solutions of Carbon Dioxide with ^{60}Co-γ-rays.

pH-Dependence of the Yields of Formic Acid as a Function of Radiation Dose

Dose (10^{16} eV ml^{-1})	G(Formic Acid)			
	pH = 2.0	pH = 4.0	pH = 7.0	pH = 3.8*
57	0.25	0.17	0.04	0.21
228	0.08	0.06	0.05	0.11

* In the presence of 10^{-3} M $FeSO_4$.

method of Grant,[4] showed a strong pH-dependence. In the presence of ferrous ions, however, the yields were found to be greater; which is in agreement with Garrison's observations.

Yields of hydrogen gas from aqueous CO_2 solutions irradiated at various pH's are shown in Table 2. The yield dose plots were non-linear falling

19

TABLE 2

Irradiation of Aqueous Solutions of Carbon Dioxide with ^{60}Co-γ-rays.
pH-Dependence of the Yields of Hydrogen as a Function
of Radiation Dose

Dose (10^{16} x eV ml^{-1})	G(Hydrogen)				
	pH = 2	pH = 4.0	pH = 7.0	pH = 10.5	pH = 3.8*
57	1.58	0.74	0.67	0.51	1.12
228	1.00	0.51	0.49	0.32	0.75

* In the presence of 10^{-3} M $FeSO_4$.

off with increasing dose. At the lowest doses used (5.7×10^{17} eV ml^{-1}) the yield for hydrogen was $G(H_2) = 1.58$ at pH 2, while at pH 10.5, it had decreased to $G(H_2) = 0.51$.

These results clearly indicate that the hydrogen atom procursor formed in the radiolysis of water can react with CO_2.

Carbon monoxide could not be detected in irradiated CO_2 solutions, over the range pH 2 to 10.9. However, small amounts of CO ($G = 0.1$) were found on irradiation (5.7×10^{17} eV ml^{-1}) in the presence of ferrous ion (10^{-3} M, $FeSO_4$) saturated with CO_2 at pH 3.75. This would suggest the posibility

[4] W. M. Grant, Industr. Engng. Chem. (Analyt.) 19, 206 (1947).

1960

that carbon monoxide can be an intermediate in the radiolysis of solutions of carbon dioxide, the ferrous ions, no doubt, preventing reactions between CO and radiation-produced radicals.

Preliminary experiments have been carried out with solutions saturated with mixtures of CO_2 and O_2 and it was found that yields of formaldehyde were much lower than obtained in the absence of oxygen. This effect of oxygen is in keeping with the fact that the radiation-produced hydrogen species are involved in the formation of the organic products.

The mechanism of these reactions is, as yet, far from clear. There are, however, a few points which can be stated with some certainty.

It appears that the radiation-induced process is the reduction of the carbon dioxide by the self-trapped electron (negative polaron)[5,6] and by hydrogen atom, leading to the formation of carbon monoxide which then could be further reduced either by polarons or hydrogen atoms to give the CHO radical. Once the latter radicals have been formed, the route to the aldehyde would be fairly obvious as the aldehyde could be formed by disproportionation of two CHO radicals or to further reduction of the CHO radical.

It appears, however, that there is also a second route for the formation of organic products, i.e. from the carbonate ion in alkaline solution, possibly by reaction with an OH radical.

The formation of the formic acid, on the other hand, is likely to proceed directly from the CO_2^-, the latter leading to the COOH radical which

---

[5] J. Weiss, Nature, Lond. 186, 751 (1960).

[6] J. T. Allan and G. Scholes, Nature, Lond. 187, 218 (1960).

then would lead to formic acid and possibly also to oxalic acid.

Photochemical Experiments

As has been shown above carbon dioxide in aqueous solution can be reduced by electron transfer and by hydrogen atoms produced by ionizing radiations. It, therefore, seemed quite likely that this reduction could also be carried out by hydrogen atoms produced photochemically and/or by electronically excited species.[7] Solutions of ferrous sulphate (10^{-2} M to 10^{-1} M) were saturated with carbon dioxide (1 atm) or irradiated with the unfiltered light from a low pressure mercury lamp and with the mercury resonance line (2537 Å) using a $CoSO_4$ - $NiSO_4$ solution as a filter. After irradiation the solutions were again analysed for formaldehyde in the manner described above. For example, 10^{-2} M $FeSO_4$ solution saturated with carbon dioxide (pH 3) was irradiated with the unfiltered u.v. light (approximately 5×10^{-7} E ml^{-1} min^{-1}.), after 10 min irradiation, 1.6×10^{-4} moles aldehyde/l. were produced. Similar results were also obtained if the ferrous sulphate was replaced by potassium iodide solutions.[8] It is quite clear that the reduction of carbon dioxide by u.v. radiation can be brought about by any suitable substances which will produce hydrogen atoms or an excited species which can reduce CO_2 to CO_2^- by an electron transfer process.

A full account of this work, together with a discussion of the mechanism of the reduction of carbon dioxide in solution, will be published elsewhere.

---

[7] J. Weiss, Nature,Lond. 136, 794 (1935); R. H. Potterill, J. O. Walker and J. Weiss, Proc.Roy.Soc. A 56, 561 (1936); T. Rigg and J. Weiss, J.Chem.Phys. 20, 1194 (1952).

[8] J. Franck and F. Haber, Sitzber.Preuss.Akad.Wiss. 250 (1931); T. Rigg and J. Weiss, J.Chem.Soc. 4198 (1952); F.H.C. Edgecombe and R.G.W. Norrish, Proc.Roy.Soc. A 253, 154 (1959).

We should like to thank Mr. H. P. Lehmann, who has carried out some of the photochemical experiments.

One of us (N.G.) would like to thank the International Atomic Energy Agency (Vienna) for the award of a Fellowship.

We should also like to express our thanks to the Rockefeller Foundation and to the North of England Council of the British Empire Cancer Campaign for financial support.

1960

Tetrahedron Letters No. 18, pp. 24-27, 1960. Pergamon Press Ltd. Printed in Great Britain

THE TOTAL SYNTHESIS OF A DEGRADATION PRODUCT OF PHYLLOCLADENE

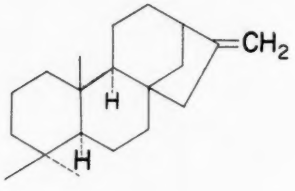
Richard B. Turner and Philip E. Shaw

Department of Chemistry, Rice University

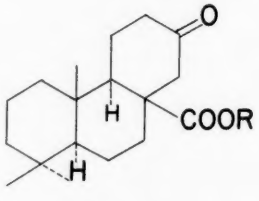
Houston, Texas

(Received 27 June 1960)

PERMANGANATE oxidation of phyllocladene (I) affords, among other products, the keto acid IIa, convertible into keto ester IIb, m. p. 161-162°, $[\alpha]_D$ -15° ($CHCl_3$), [1,2] for which optical rotatory dispersion evidence [2,3] suggests the stereochemistry indicated. We wish to report the total synthesis of IIb.



I



IIa, R=H

IIb, R=CH_3

---

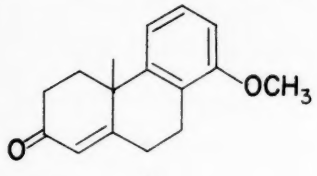
1 C. W. Brandt, New Zealand J. Sci. Technol. 34B, 46 (1952); L. H. Briggs, B. F. Cain, B. R. Davis and J. K. Wilmshurst, Tetrahedron Letters No. 8, 8 (1959).

2 P. K. Grant and R. Hodges, Tetrahedron 8, 261 (1960).

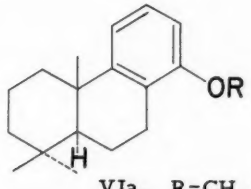
3 C. Djerassi, M. Cais and L. A. Mitscher, J. Amer. Chem. Soc. 81, 2386 (1959).

1960

The Cornforth-Robinson ketone (III) [4] was dimethylated with methyl iodide in the presence of potassium t -butoxide and gave 1, 2, 3, 4, 9, 12-hexahydro-8-methoxy-1, 1, 12-trimethyl-2-oxophenanthrene (IV), m.p. 109.5-110-5°, $\lambda_{max}^{CS_2}$ 5.84μ (Found: C, 79.66; H, 8.13. $C_{18}H_{22}O_2$ requires: C, 79.96; H, 8.20). Palladium-catalyzed hydrogenation of IV afforded the corresponding dihydro derivative (V), m.p. 90-93° (Found: C, 79.30; H, 8.63. $C_{18}H_{24}O_2$ requires: C, 79.37; H, 8.88), convertible by Clemmensen reduction into trans - 1, 2, 3, 4, - 9, 10, 11, 12-octahydro-8-methoxy-1, 1, 12-trimethylphenanthrene (VIa), m.p. 114-115° (Found: C, 83.48; H, 10.17. $C_{18}H_{26}O$ requires: C, 83.67; H, 10.14). The free phenol (VIb), m.p. 146-148° (Found: C, 83.62; H, 10.20. $C_{17}H_{24}O$ requires: C, 83.55; H, 9.90) was



III



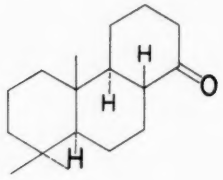
VIa, R=CH_3
VIb, R=H

obtained by treatment of VIa with hydriodic acid in acetic acid. Hydrogenation of VIb over nickel gave a mixture of two epimeric, saturated alcohols, VIIa, m. p. 118-119° (Found: C, 81.76; H, 12.37.

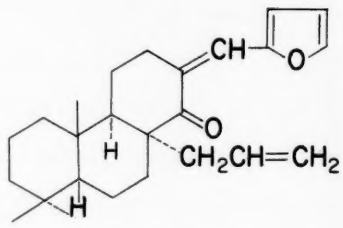
---

[4] J. W. Cornforth and R. Robinson, J. Chem. Soc. 1855 (1949).

$C_{17}H_{30}O$ requires: C, 81.53; H, 12.08), and VIIb, m.p. 99-100° (Found: C, 81.67; H, 11.99). On treatment with chromic acid in acetic acid VIIa and VIIb are both transformed into the base-stable ketone VIII, m.p. 67-68°, $\lambda_{max}^{CS_2}$ 5.83μ (Found: C, 82.09; H, 11.50. $C_{17}H_{28}O$ requires: C, 82.20; H, 11.36).



VIII



X

Condensation of VIII with furfuraldehyde yields the corresponding furfurylidene derivative (IX), m. p. 87.5-88°, $\lambda_{max}^{CS_2}$ 5.96μ (Found: C, 80.99; H, 9.42. $C_{22}H_{30}O_2$ requires: C, 80.93; H, 9.26), which is further transformed into X, m.p. 108-108.5°, $\lambda_{max}^{CS_2}$ 5.96, 10.08, 10.94μ (Found: C, 81.71; H, 9:30. $C_{25}H_{34}O_2$ requires: C, 81.92; H, 9.35) by treatment with allyl bromide and potassium t -butoxide. Ozonization of X, followed by treatment with chromic acid and esterification with diazomethane, yields an amorphous triester, which undergoes Dieckmann cyclization, hydrolysis, and decarboxylation to d, l-IIb, m. p. 130-131° (Found: C, 74.78; H, 9.94. $C_{19}H_{30}O_3$ requires: C, 74.47; H, 9.87). The infrared spectrum (CS_2) of the latter product was identical with that of the optically active degradation product of phyllocladene.

Resolution of the alcohol VIIa, obtained for this purpose by lithium aluminum hydride reduction of VIII, was accomplished by esterification

1960

with 3α-acetoxy-11-ketoetiocholanic acid.[5] The ester with lower rotation, m. p. 237-238°, $[\alpha]_D$ + 28° ($CHCl_3$) (Found: C, 76.69; H, 9.80. $C_{39}H_{60}O_5$ requires: C, 76.93; H, 9.93), was saponified and gave l -VIIa, m.p. 109-110°, $[\alpha]_D$ - 29° ($CHCl_3$). This substance and the succeeding optically active compounds were not analyzed; their constitutions were established by the identity of the infrared absorption spectra (CS_2 solution) with the spectra of the appropriate analyzed, optically inactive derivatives. Oxidation of l - VIIa afforded l - VIII, m.p. 87.5-88° $[\alpha]_D$ - 18° ($CHCl_3$) (negative Cotton effect)[6] which gave d - IX, m. p. 122.5-123°, $[\alpha]_D$ + 41° ($CHCl_3$), on condensation with furfuraldehyde. Alkylation to l - X, m. p. 88-88.5°, $[\alpha]_D$ - 115° ($CHCl_3$), oxidation, and cyclization completed the synthesis. The synthetic product l - IIb, m.p. 159-160°, $[\alpha]_D$ -12° ($CHCl_3$), did not depress the melting point of a specimen, m.p. 159-161°, $[\alpha]_D$ -11° ($CHCl_3$), obtained from phyllocladene, and the infrared spectra of the two samples were identical.

It is a pleasure to acknowledge financial support of this investigation by the Eli Lilly Co., and by the National Institutes of Health.

---

5 J. von Euw, A. Lardon and T. Teichstein, Helv. Chim. Acta 27, 1287 (1944); R. B. Turner, V. R. Mattox, W. F. McGuckin and E. C. Kendall, J. Am. Chem. Soc. 74, 5814 (1952).

6 We are indebted to Dr. Max A. Marsh, Eli Lilly and Co., Indianapolis, for this result, from which the conclusion is drawn that l - VIII possesses the required absolute configuration, cf. C. Djerassi, Optical Rotatory Dispersion, McGraw-Hill, New York (1960), p. 178, and C. Djerassi and W. Klyne, Chemistry and Industry 988 (1956).

Tetrahedron Letters No. 18, pp. 28-30, 1960. Pergamon Press Ltd. Printed in Great Britain

AMINOOXY-PEPTIDE DERIVATIVES OF DL-CANALINE

Max Frankel, Y. Knobler and G. Zvilichowsky

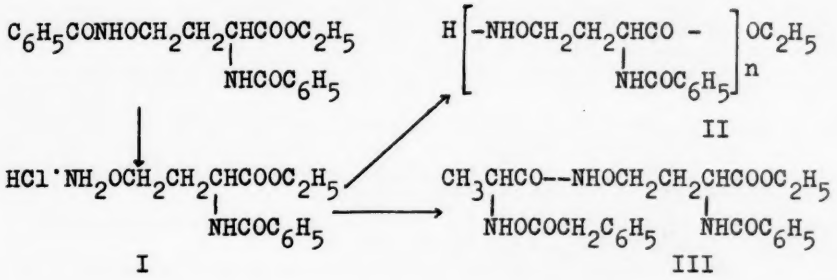
Department of Organic Chemistry, Hebrew University, Jerusalem

(Received 7 July 1960)

ETHYL N^{α},N^{ω}-dibenzoyl-DL-canalinate (DL-α-benzamido-γ-benzamido-oxybutyric acid ethyl ester), prepared by condensation of benzhydroxamic acid with α-benzamido-γ-halogenobutyric acid ethyl ester[1], could be freed from the benzoyl rest attached to the γ-aminooxy group without cleavage of the α-benzamidic linkage or hydrolysis of the ester, by refluxing in 10% ethanolic hydrogen chloride, resulting in ethyl N^{α}-benzoyl-DL-canalinate hydrochloride (I) (m.p. 162°; anal. found: C,50.9; H,6.3; N,9.5; Cl,12.0; OC_2H_5,14.8. $C_{13}H_{19}N_2O_4Cl$ requires C,51.5; H,6.2; N,9.3; Cl,11.7; OC_2H_5, 14.9; the compound gave the orange-red colour with alkaline picrate (Jaffe's test) specific for the free aminooxy group, and a negative ninhydrin test). The canalinate (I) served for the following reactions carried out on the γ-aminooxy group: intermolecular peptidic selfcondensation, intramolecular condensation, peptidic acylation by an N-protected amino acid and amidination to the guanidinoxy derivative.

---

[1] Y. Knobler and M. Frankel, J. Chem. Soc. 1629 (1958).



When ethyl N^{α}-benzoyl-DL-canalinate was freed from hydrogen chloride with potassium acetate and then refluxed in ethanol for a few hours, a condensation product was obtained, from which an (average) aminooxy-tripeptide (II) was isolated (m.p. 95-100°; anal. found: C,60.1; H,5.8; N,11.9; OC_2H_5,6.9. $C_{35}H_{42}N_6O_{10}$ requires C,59.5; H,5.9; N,11.9; OC_2H_5,6.4).

The ethyl N^{α}-benzoyl-N^{ω}-[N^{α}-benzoyl-N^{ω}-(N^{α}-benzoyl-DL-canalyl)-DL-canalyl]-DL-canalinate (II) represents a new type of a peptidic compound, linking the carboxyl group of an α-amino acid with the aminooxy group of the α-amino acid canaline, which occurs in nature in the L-form.

On the other hand, condensation of the free ester of I according to the high dilution principle leads through intramolecular cyclisation to the lactamic N-benzoyl derivative of DL-canaline (N^{α}-benzoyl-DL-homocycloserine); this is indicated by the specific blue colour test reaction with sodium nitritopentacyanoferroate[2].

---

[2] L.R. Jones, Anal. Chem. 28, 39 (1956).

The aminooxy peptidic linkage was also built up between the canalinate I and another α-amino acid, e.g. DL-alanine. After liberation of I by triethylamine in methylene chloride, the free canalinate was condensed with N-benzyloxycarbonyl-DL-alanine by the aid of N,N'-dicyclohexyl carbodiimide, resulting in ethyl N^{α}benzoyl-N^{ω}-(N-benzyloxycarbonyl-DL-alanyl)-DL-canalinate (III) (found: N,9.1; OC_2H_5,9.4. $C_{24}H_{23}N_3O_7$ requires N,9.0; OC_2H_5,9.7; Jaffe's test - negative).

The N^{α}benzoyl-DL-canalinate freed as above from I, was also used for amidination of the aminooxy group by the aid of S-methylisothiourea sulphate. The DL-canavanine derivative thus obtained gives the characteristic magenta colour reaction of the guanidinoxy group of canavanine, tested with activated sodium nitroprusside[3].

Syntheses parallel to those above were also carried out with aminooxyacetic acid ethyl ester, prepared by condensation of benzhydroxamic acid with ethyl bromoacetate and removal of the benzoyl rest, in the same manner as for I.

---

[3] W.R. Fearon and E.A. Bell, Biochem. J. 59, 221 (1955).

Tetrahedron Letters No. 18, pp. 31-35, 1960. Pergamon Press Ltd. Printed in Great Britain

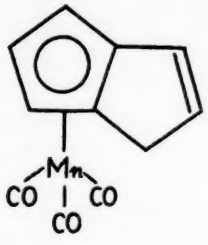
THE SYNTHESIS OF TWO DIHYDROPENTALENYL DERIVATIVES[1]

A. Modiano and M. Cais[2]

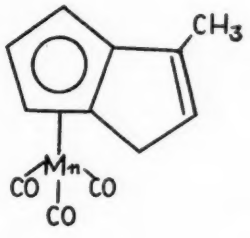
Department of Chemistry, Israel Institute of Technology, Haifa.

(Received 7 July 1960)

Recently[3] we reported the preparation of several new derivatives of cyclopentadienylmanganese tricarbonyl, to serve as model compounds towards an eventual synthesis of a potential pentalene system. The basic idea of this approach was that metal complexing the double bonds of one ring might stabilize the system sufficiently to enable one to proceed with the introduction of the double bonds (or potential double bonds) in the second cyclopentadiene ring of pentalene. In the present note we wish to report the synthesis of two dihydropentalenyl derivatives I and II



I



II

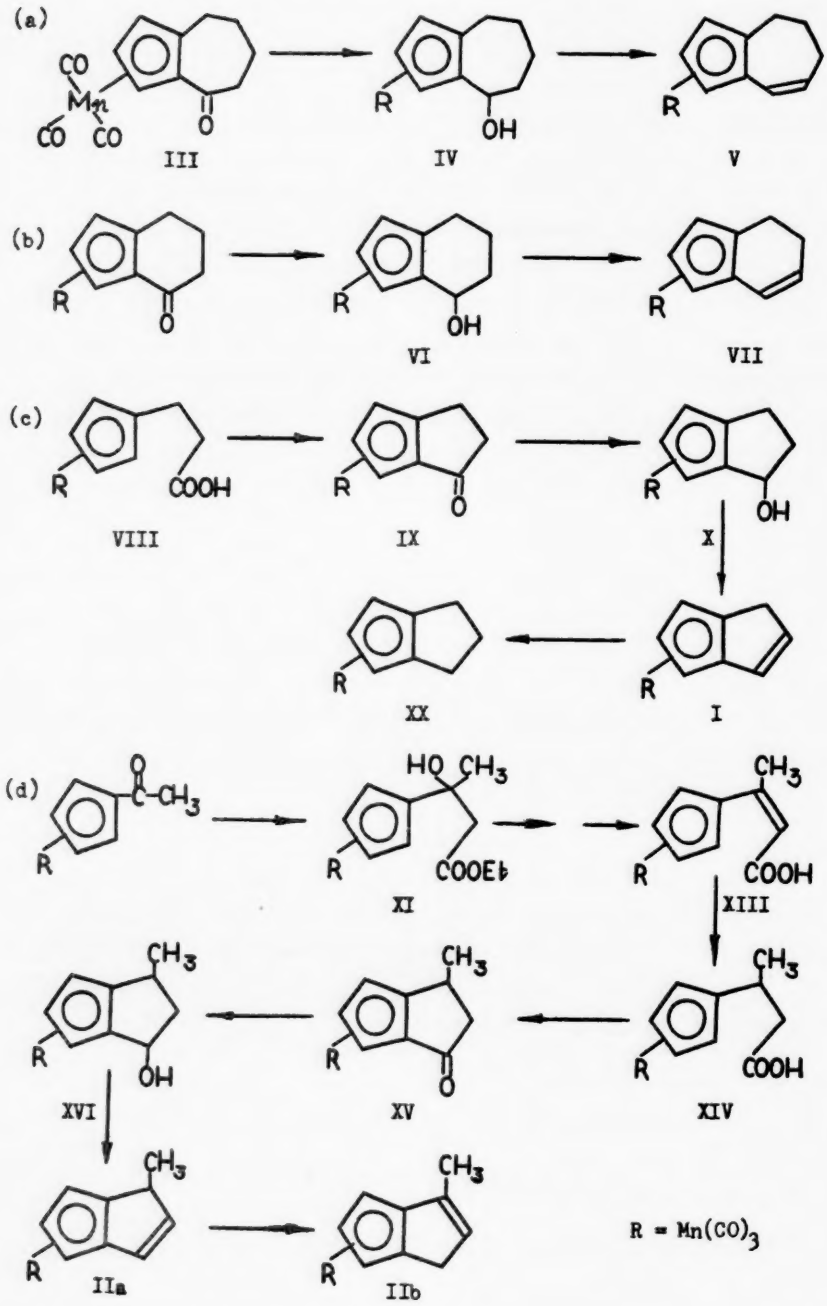
Reduction of ketone III[3] with aluminum isopropoxide yielded 60% of the alcohol IV, m.p. 90-91° (Found: C, 54.12; H, 4.70; Mn, 19.27. $C_{13}H_{13}MnO_4$ requires: C, 54.18; H, 4.55; O, 19.02%).

---

[1] Presented in part at the meeting of Israel Chemical Society, Jerusalem, April 19-20, 1960.

[2] To whom inquiries should be addressed.

[3] M. Cais and A. Modiano, Chem. and Ind. 202 (1960).


(a)
CO
Mn
CO CO
O
R
OH
III
IV
V
(b)
R
O
OH
VI
VII
(c)
R
COOH
O
OH
VIII
IX
X
XX
I
(d)
O
C-CH3
R
HO CH3
COOEt
CH3
COOH
XI
XIII
CH3
R
OH
O
XVI
XV
XIV
CH3
R
IIa
IIb
R = Mn(CO)3

1960

Dehydration of IV yielded 98% of the tetrahydroazulenylmanganese tricarbonyl derivative V, b.p. 90°/0.03 mm. (Found: C, 57.41; H, 4.30; Mn, 20.26. $C_{13}H_{11}MnO_3$ requires: C, 57.79; H, 4.10; Mn, 20.34%). (No OH absorption bands in infrared spectrum). By the same reaction sequence we obtained in 90% yield (after dehydration) the dihydroindenylmanganese tricarbonyl compound VII, b.p. 78-80°/0.05 mm. (Found: Mn, 21.49. $C_{12}H_9MnO_3$ requires: Mn, 21.45%).

The experience gained with the model compounds enabled us to proceed with reaction sequence (c). Cyclization of the propionic acid derivative VIII[3] produced the ketone IX in 60% yield, m.p. 102-104° (Found: C, 51.30; H, 2.61; Mn, 20.99. $C_{11}H_7MnO_4$ requires: C, 51.19; H, 2.73; Mn, 21.29%). Reduction to the alcohol and dehydration produced in 95% yield (calculated on dehydration reaction) dihydropentalenylmanganese tricarbonyl I, b.p. 74-76°/0.05 mm. (Found: C, 54.71; H, 2.78; Mn, 22.52. $C_{11}H_7MnO_3$ requires[6]: C, 54.57; H, 2.92; Mn, 22.69%). The infrared spectrum[4] of I was similar but not identical with that of the compound from the reaction of acetylene with manganese carbonyl and to which the authors have recently[5] ascribed structure I[6]. In the catalytic hydrogenation of I (PtO_2 catalyst) one mole of hydrogen was absorbed and the infrared spectrum[4] of the reduced compound was identical with that of the compound reported[5] during the preparation of this manuscript and to which the same structure XI was ascribed.

Reaction scheme (d) shows the route for the synthesis of the methyl dihydropentalenyl derivative II. The Reformatzky reaction on (acetylcyclopentadienyl)manganese tricarbonyl[7] yielded 98% (crude) of

---

[4] We wish to thank Dr. W.B. Ligett, Director, Chemical Research, Ethyl Corporation, Detroit, Mich., for kindly sending us copies of the infrared spectra of the acetylene-manganese carbonyl derivatives[5].

[5] T.H. Coffield, K.G. Ihrman and W. Burns, J. Am. Chem. Soc. 82, 1251 (1960).

[6] The calculated analysis for $C_{11}H_7MnO_3$ as given by above authors[5] appears to be in error.

[7] J. Kozikowski, R.E. Maginn and M. Sizen-Klove, J. Am. Chem. Soc. 81, 2995 (1959).

the β-hydroxy ester XI, m.p. 42.5-43.5°. (Found: C, 50.23; H, 4.59; Mn, 16.59. $C_{14}H_{15}MnO_6$ requires: C, 50.31; H, 4.52; Mn, 16.44%). Dehydration of XI afforded in nearly quantitative yield the corresponding α-β-unsaturated ester XII, m.p. 73.5-74.5° (Found: C, 53.45; H, 3.97; Mn, 17.19. $C_{14}H_{13}MnO_5$ requires: C, 53.18; H, 4.14; Mn, 17.38%). Hydrolysis of XII yielded 66% of the α-β-unsaturated acid XIII, m.p. 171-172.5° (Found: C, 50.19; H, 3.22; Mn, 19.13. $C_{12}H_9MnO_5$ requires: C, 50.02; H, 3.15; Mn, 19.07%). Hydrogenation of XIII (Raney Nickel catalyst) yielded 92% of the butyric acid derivative, XIV, m.p. 105-107° (Found: C, 49.51; H, 3.66; Mn, 18.84. $C_{12}H_{11}MnO_5$ requires: C, 49.67; H, 3.82; Mn, 18.93%). Cyclization to the ketone XV proceeded in 93% yield, b.p. 104°/0.02 mm. (Found: C, 52.84; H, 3.38; Mn, 20.09. $C_{12}H_9MnO_4$ requires: C, 52.96; H, 3.33; Mn, 20.19%). The aluminium isopropoxide reduction to the alcohol XVI proceeded in 98% yield (crude), b.p. 108°/0.04 mm. (Found: C, 52.77; H, 4.10; Mn, 19.99. $C_{12}H_{11}MnO_4$ requires: C, 52.57; H, 4.05; Mn, 20.04%). Dehydration of XVI gave a high yield (98%) of the methyl dihydropentalenyl derivative II, b.p. 98°/0.1 mm. (Found: C, 56.38; H, 3.65; Mn, 21.05. $C_{12}H_9MnO_3$ requires: C, 56.27; H, 3.54; Mn, 21.45%). It is likely that the olefinic double bond in IIa migrates to the position of highest substitution, IIb and we are currently investigating this possibility.

It is interesting to speculate on the possible contributions of the resonating forms of XIXa and XIXb, with eight Π electrons available, to the electronic structure of compounds I and II.

XIXa XIXb

Investigations are in progress for finding methods to transform the organometallic pentalenyl derivatives I and II into the metal-free hydrocarbons.

Acknowledgment. We wish to thank the Israeli Ministry of Commerce and Industry for financial support and Ethyl Corporation, Detroit, Mich., U.S.A. for generous supplies of cyclopentadienylmanganese tricarbonyl.

1960

Tetrahedron Letters No. 18, pp. 36-38, 1960. Pergamon Press Ltd. Printed in Great Britain

THE ISOLATION OF SPERMIDINE BY DEGRADATION OF LUNARINE*

Pierre Potier, Jean Le Men, Maurice-Marie Janot and Peter Bladon**

Laboratoire de Pharmacie Galénique, Faculté de Pharmacie, Paris

(Received 11 July 1960)

RECENTLY, we have reported the formation of an amine by alkaline degradation,[1] and by acid hydrolysis[2] of the alkaloid lunarine ($C_{25}H_{31}O_4N_3$). We ascribed to this amine the molecular formula $C_5H_{14}N_2$ on the basis of the analysis of the hydrochloride. Further studies have shown that this formula is incorrect and have proved the identity of the amine with spermidine (I).

A B A A B B A

$$H_2N.CH_2.CH_2.CH_2.NH.CH_2.CH_2.CH_2.CH_2.NH_2$$

I

It was found that the gas chromatographic behaviour of the amine was similar to that of spermidine. The melting point of the amine hydrochloride was identical with that of, and showed no depression on admixture with, an authentic sample of spermidine trihydrochloride. Furthermore the infrared spectra of the hydrochloride, picrate, and chloraurate of the amine were

---

* This letter should be regarded as the fourth paper in the series "Alcaloides du Lunaria biennis Moench" and the second part in the series "The Chemistry of Lunaria Alkaloids".

** Chemistry Department, The Royal College of Science and Technology, Glasgow.

1 P. Potier and J. Le Men, Bull. Soc. Chim. Fr. 456 (1959).

2 P. Bladon, R. Ikan, F. S. Spring and A. D. Tait, Tetrahedron Letters No. 9, 18 (1959).

TABLE 1

Salts of Amine Derived from Lunarine and of Spermidine

	Spermidine	Amine from lunarine	
	m.p.	m.p.	Analysis
Trihydrochloride	255-257° cf. 256-258° [4]	258°	Found: C, 32.8; H, 8.7; N, 16.4; Cl, 41.2. Calc. for $C_7H_{22}N_3Cl_3$: C, 33.0; H, 8.7; N, 16.5; Cl, 41.8%
Picrate	210-212° cf. 210-212° [3,4]	210-212°	Found: C, 35.9; H, 3.45; N, 19.8. Calc. for $C_{25}H_{28}N_{12}O_{21}$: C, 36.1; H, 3.4; N, 20.2%
Chloroaurate	207-212° dec. cf. 220-222° [3] 219-220.5° [4]	207-212° dec.	Found: Au, 50.2. Calc. for $C_7H_{22}N_3Cl_{12}Au_3$: Au, 50.7%.

[3] H. W. Dudley, O. Rosenheim and W. W. Starling, Biochem. J. 21, 97 (1927).

[4] M. Danzig and H. P. Schultz, J. Amer. Chem. Soc. 74, 1836 (1952).

identical with those of the corresponding salts of spermidine. (See Table 1). The molecular weight of the amine determined by mass spectrometry was 145 (Calc. for $C_7H_{19}N_3$:145).

Difficulty has been encountered in reconciling the proton magnetic resonance spectrum of the amine hydrochloride with any structure based on $C_5H_{14}N_2$. The chief features of this spectrum (obtained at 60 mc/s in D_2O) are two groups of signals centred at 100 (A) and 180 c/s (B) (relative to the HDO peak); the ratio of the areas of these two groups (A:B) is 4:3, which indicates that the total number of hydrogens bonded to carbon is a multiple of 4 + 3. The structure of spermidine agrees well with these results: the signal at 100 c/s (relative area 4) arises from the hydrogens of the four CH_2 groups attached to nitrogen atoms, while the signal at 180 c/s (area 3) is due to the hydrogens of the three CH_2 groups attached only to carbon. (These assignments are indicated in the formula of spermidine, I.)

This is the second isolation of the typical animal base, spermidine, by degradation of a plant alkaloid: in the last few months, Baumann et al.[5] have encountered spermidine as a degradation product of the alkaloid palustrine, for which they suggest a macrocyclic structure. It seems probable that also in lunarine, which is a monoacidic secondary amine, there is present a macrocyclic system, the two terminal nitrogens of the spermidine moiety being attached by amide links to the rest of the molecule.

We are indebted to Dr. LeRoy Johnson of Varian Associates, Palo Alto, California, for the n.m.r. spectrum of the amine hydrochloride, and to Dr. R.I. Reed and Mr. J.M. Wilson of Glasgow University for the mass spectrum of the amine.

---

[5] C.G. Baumann, W. Dietsche and C.H. Eugster, Chimia 14, 85 (1960); cf. Angew. Chem. 72, 270 (1960).

1960

Tetrahedron Letters No. 19, pp. 1-5, 1960. Pergamon Press Ltd. Printed in Great Britain

THE STRUCTURE OF ANGUSTIFOLINE*

Léo Marion[1], M. Wiewiorowski[2] and M.D. Bratek[2]

(Received 11 July 1960)

Angustifoline ($C_{14}H_{22}ON_2$) is an alkaloid that has been isolated from three plants: Lupinus angustifolius, L. polyphyllus and L. albus.[3] It is a monoacidic base containing a lactamic carbonyl and a double bond. Both functions are indicated in the infrared spectrum and their presence confirmed by catalytic hydrogenation which in neutral solution gives dihydroangustifoline, $C_{14}H_{24}ON_2$, and in acid solution produces dihydrodesoxyangustifoline, $C_{14}H_{26}N_2$, a diacidic base.[4] Wiewiorowski, Galinovsky

---

* Contribution No.5762 from the National Research Council.

[1] Division of Pure Chemistry, National Research Council, Ottawa, Canada.

[2] Biochemical Laboratory, Institute of Plant Breeding, Polish Academy of Sciences, Poznan, Poland.

[3] M. Wiewiorowski and M.D. Bratek, Bull. acad. polon. sci. Kl II, 4, 3 (1956).

[4] M. Wiewiorowski, F. Galinovsky and M.D. Bratek, Monatsh. 88, 663 (1957).

and Bratek[4] who carried out preliminary work on the alkaloid concluded from chemical and spectral evidence that it contained a 1,2-disubstituted-piperid-6-one.

The present investigation has made it possible to arrive at the total structure of the alkaloid. According to the infrared and NMR spectra of angustifoline, the double bond must be present in a vinyl group, and the infrared spectrum of dihydroangustifoline no longer shows the bands characteristic of the vinyl group, while its NMR spectrum contains the signal typical of a methyl group (3.83 p.p.m.). The base must have a tricyclic structure.

The basic nitrogen is secondary and reacts with formic acid producing N-formylangustifoline, $C_{15}H_{22}O_2N_2$, m.p. 136°, which in the infrared contains bands at 1645 and 1675 cm^{-1} attributable to the original lactamic carbonyl and to the new carbonyl group. On the other hand, angustifoline I reacts with a mixture of formic acid and formaldehyde in a different way. The reaction gives rise to a product IIb ($C_{15}H_{24}O_2N_2$) isomeric with the naturally-occurring 13-hydroxylupanine. The product melts at 190-191°, and its infrared absorption spectrum differs from that of 13-hydroxylupanine only in the region 1000-1100 cm^{-1}. Since these differences are the same

1960

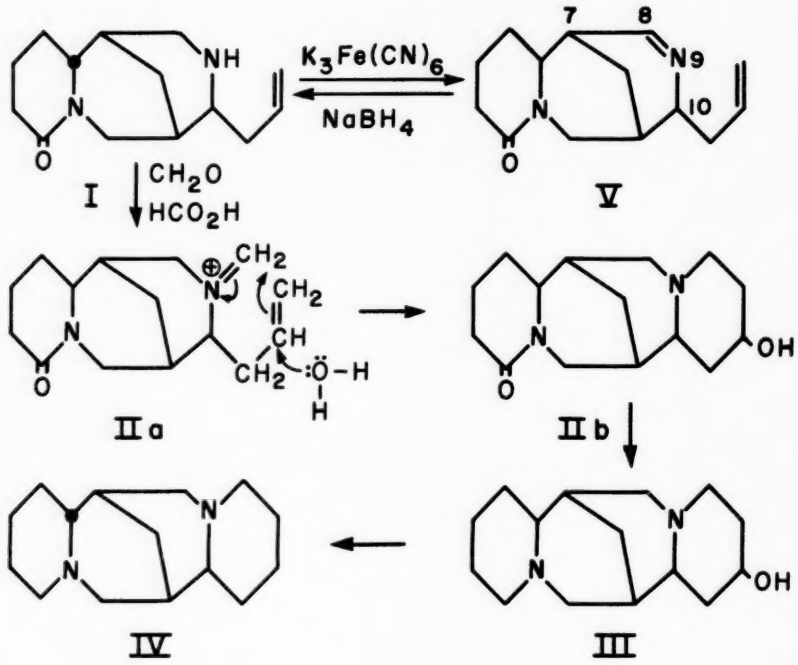
as those observed between the spectra of 13-epihydroxysparteine[8] and 13-hydroxysparteine, it is assumed that IIb is 13-epihydroxylupanine. This conclusion finds confirmation in the catalytic hydrogenation of IIb which converts it into 13-epihydroxysparteine III, m.p. 171-172°, the infrared spectrum of which is identical with that published by Bohlmann et al.[8] who prepared this compound.

Dehydration of III with phosphorus pentoxide at 140° followed by hydrogenation over platinum gave (—)-sparteine (IV) which was characterized as the dipicrate, m.p. 206°, either alone or in admixture with an authentic specimen. The identity was also established by comparison of the X-ray powder pattern of the picrate of IV with that of (—)-sparteine dipicrate: they were superimposable.

The foregoing series of reactions makes it possible to assign to angustifoline the total structure I, and to represent the transformations as in the following scheme:

---

[8] F. Bohlmann, E. Winterfeldt and H. Brackel, Chem. Ber. 91, 2194 (1958).



The anhydronium salt IIa of N-hydroxymethylangustifoline has not been isolated, although the presence of an intermediate is indicated on the paper chromatogram of the crude product of the reaction.

Oxidation of the alkaloid with potassium ferricyanide or with N-bromosuccinimide gives rise to dehydroangustifoline V ($C_{14}H_{20}ON_2$), m.p. 105°, which is converted back to angustifoline by the action of sodium borohydride or to dihydroangustifoline by catalytic

hydrogenation. The perchlorate of dehydroangustifoline shows in the infrared a band at 1680 cm^{-1} characteristic of an enamine salt. That the new double bond is at C_8 and not at C_{10} is shown by the signals at -3.15 p.p.m. relative to tetramethylsilane in the NMR spectrum. With the double bond at C_8, the group $\underset{H}{>}C=N-$ is present and the signal of the H in this group would be expected to appear in that region somewhat analogous to an aldehyde H.[6]

Dehydroangustifoline V has been found to be identical with the alkaloid "w-102" isolated from L. angustifolius by Bratek and Wiewiorowski.[7]

One of us (M.W.) wishes to thank the Rockefeller Foundation for a fellowship, and the National Research Council of Canada for the generous hospitality afforded during May 1959 - May 1960 when this work was completed.

---

[6] G. van Dyke Tiers, Organic Section Exploratory NMR studies, Project 737602, Minnesota Mining and Manufacturing Compay.

[7] M.D. Bratek and M. Wiewiorowski, Roczniki Chem. 33, 1187 (1959).

Tetrahedron Letters No. 19, pp 6-15, 1960. Pergamon Press Ltd. Printed in Great Britain

THE MECHANISM OF ISOTOPE EXCHANGE REACTIONS OF DIALKYLMERCURY AND ALKYLMERCURIC HALIDES[1]

O. A. Reutov, T. P. Karpov, E. V. Uglova

and V. A. Malyanov

The M.V.Lomonosov Moscow University, Chemical Department

(Received 13 July 1960)

IN the course of systematic investigation of isotope exchange reactions of organomercuric compounds one of the present authors and his coworkers[2-6] have described the following types of reactions:

$$RHgX + {}^{203}Hg \rightleftharpoons R{}^{203}HgX + Hg \qquad \text{(ref. 2)}$$

$$R_2Hg + {}^{203}Hg \rightleftharpoons R_2{}^{203}Hg + Hg \qquad \text{(ref. 3)}$$

$$RHgX + {}^{203}HgX_2 \rightleftharpoons R{}^{203}HgX + HgX_2 \qquad \text{(ref. 4)}$$

$$RHgX + R'{}^{203}HgX \rightleftharpoons R{}^{203}HgX + R'HgX \qquad \text{(ref. 5)}$$

$$R_2Hg + R'_2{}^{203}Hg \rightleftharpoons R_2{}^{203}Hg + R'_2Hg \qquad \text{(ref. 6)}$$

---

[1] Translated by A. L. Pumpiansky, Moscow.

[2] O.A. Reutov and G.M. Ostapchuk, Zh. Obschei Khim. 29, 1614 (1959).

[3] O.A. Reutov and G.M. Ostapchuk, Dokl. Akad. Nauk SSSR 117, 826 (1957); O.A. Reutov, Izv. Akad. Nauk SSSR, Otdel. chim. nauk 684 (1958).

[4] O.A. Reutov, T.A. Smolina, Chang Tsei U and Ju.P. Bubnov, Dokl. Visshei Shkoly No. 2, 324 (1958); O.A. Reutov, P. Knoll and Chang Tsei U, Dokl. Akad. Nauk SSSR 120, 1052 (1958).

[5] O.A. Reutov, Angew. Chem. No. 6, 198 (1960).

[6] O.A. Reutov, T.A. Smolina and Vang Hoon Hoo, Izv. Akad. Nauk SSSR, Otdel. chim. nauk 559 (1959).

Now we report on a novel isotope exchange reaction of alkylmercuric compounds:

$$R_2Hg + R^{203}HgX \rightleftharpoons R_2{}^{203}Hg + RHgX$$

$$[R = (CH_3)_2 CHCH_2CH_2\overset{*}{C}HCH_3, \quad X = Br]$$

Optically active 5-bromomercuri-2-methyl hexane and bis(2-methylhexyl-5) mercury, obtained previously, were used as starting compounds.[7] Dialkylmercury was purified by distillation at 1.10^{-4} mm and 35-40°. (Found: C, 41.85, 41.88; H, 7.63, 7.61; Hg, 50.04, 50.06%. $C_{14}H_{30}H_9$ requires C, 42.21; H, 7.58; Hg, 50.2%.)

The exchange was carried out in absolute alcohol at 60° in the dark at an equimolecular concentration of reagents (0.05 mole). The reaction mixture samples (10-12 cm^3) were diluted with petroleum ether and repeatedly washed with water to remove alcohol.

The mixture of reagents in petroleum ether was separated through a column with Al_2O_3, dialkylmercury eluated with petroleum ether and alkylmercuric bromide with diethyl ether followed by colour reaction with dithizone Dialkylmercury was converted under the action of $HgBr_2$ into alkylmercuric bromide. The radioactivity and specific rotation of the latter was then estimated. Special experiments enabled us to determine that separation and purification did not affect the angle of rotation of the compounds. Labelled alkylmercuric bromide $R^{203}HgX$ was obtained by treating dialkylmercury with $^{203}HgBr_2$. Optically active alkylmercuric bromide, labelled with ^{203}Hg, and racemic dialkylmercury were used in run 1. As the reaction proceeded a distribution of optical activity between RHgX and R_2Hg was observed. A

---

[7] O.A. Reutov and E.V. Uglova, Izv. Akad. Nauk SSSR, Otdel. chim. nauk 757 (1959).

double angle of rotation of RHgBr obtained from R_2Hg under the action of $HgBr_2$ was taken as a characteristic of the optical activity of dialkylmercury (α_{R_2Hg}).[8] RHgBr had $[\alpha]_D^{20} = \alpha_{RHgBr}$, $\alpha_{R_2Hg} = 2\alpha_{RHgBr}$.

The angles were all taken in absolute alcohol. Racemic RHgBr was used in run 2, together with optically active dialkylmercury having the angle of rotation $[\alpha]_D^{20} = -21.7^\circ$ ($\alpha_{R_2Hg} = -31.4^\circ$) and produced by treating active alkylmercuric bromide with racemic Grignard reagent:

$$\overset{*}{R}HgBr + RMgX \rightleftharpoons \overset{*}{R}HgR$$

TABLE 1

Run 1: Isotope Exchange and Radical Exchange Data[a]

Time (hr)	Isotope exchange (%)	α_{R_2Hg}	α_{RHgX}	$\alpha_{R_2Hg} + \alpha_{RHgX}$	Average sum
3	60.0	-7.6 ± 0.5[b]	-15.4 ± 0.3	-23.0 ± 0.8	21.6 ± 0.9
5	70.0	-8.3 ± 1.2	-12.2 ± 0.2	-20.5 ± 1.4	
10	97.0	-10.6 ± 0.2	-10.6 ± 0.2	-21.2 ± 0.4	

a As the reagents dissolved together on heating, the rate of exchange was at first elevated.

b Precision was calculated in terms of each measurement accuracy which was about $\pm 0.005^\circ$.

---

[8] Reaction of Alk_2Hg and $HgBr_2$ proceeds with complete retention of configuration at asymmetric carbon.[9,10]

[9] H. B. Charman, E.D. Hughes and C.K. Ingold, J. Chem. Soc. 2530 (1959).

[10] O.A. Reutov and E.V. Uglova, Izv. Akad. Nauk SSSR, Otdel. khim. nauk 1691 (1959).

TABLE 2

Run 2: Radical Exchange Data

Time (hr)	α_{RHgBr}	α_{R_2Hg}	$\alpha_{RHgBr} + \alpha_{R_2Hg}$	Angle of the reaction mixture=1	Radical exchange (%)	ln (1-F')	V!10^3 mole/ 1 hr	V!10^3 mean
I	II	III	IV	V	VI	VII	VIII	IX
2	-3.2±0.2	-28.8±0.2	-32.0±0.4		21.2	0.103	4.0	
3	-3.1±0.2	-27.6±0.4	-30.7±0.6		32.7	0.172	4.4	
4	-3.9±0.3	-26.6±0.4	-30.5±0.7	-0.452	42.4	0.240	4.6	
			-30.6 [a]					4.7±0.3
5	-	-25.8±0.4	-		50.0	0.301	4.6	
6	-4.8±0.3	-24.8±0.4	-29.6±0.7	-0.459	59.6	0.394	5.0	
			-30.4 [a]					
15	-10.8 [a]	-20.2±0.5	-31.0 [a]	-0.479	104			

[a] The angle was calculated from the angle of rotation of reaction mixture.

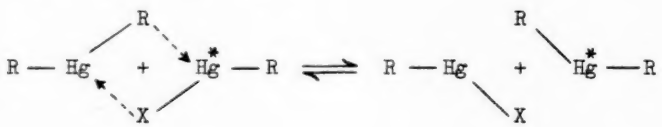
The number of optically active radicals in the reaction mixture was checked by determining α_{RHgBr} and α_{R_2Hg} for RHgBr and R_2Hg obtained from each sample. In both runs the sum of α_{RHgBr} and α_{R_2Hg} remained constant over the whole reaction (within the experimental error of $\pm$ 4 per cent).

In run 2 we also estimated the angle of rotation of the reaction mixture. This increased with time because the active radicals migrated from dialkylmercury to alkylmercuric bromide which has a greater specific angle of rotation. From these values we calculated α_{RHgBr} and $(\alpha_{RHgBr} + \alpha_{R_2Hg})$ which proved to be in good agreement with values obtained after the separation of the mixture.

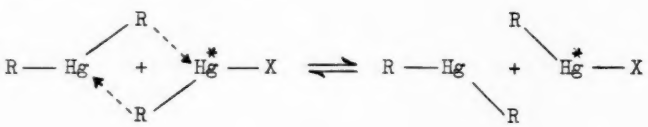
From the data listed in Tables 1 and 2 it can be seen that the isotope exchange reaction under consideration proceeds with strict retention of configuration at asymmetric carbon, the sum of $\alpha_{RHgBr} \pm \alpha_{R_2Hg}$ remaining constant during the reaction.

Let us now consider the possible mechanisms of our reaction. They seem to be limited to the following five alternatives.

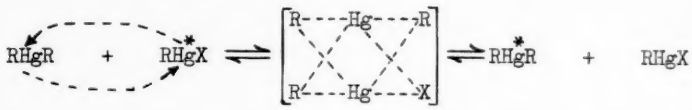
I Exchange of R to X ($R \rightleftharpoons X$)



II Exchange of R to R ($R \rightleftharpoons R$)

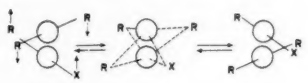


III Exchange of Hg to $\overset{*}{Hg}$



In this case both radicals in R_2Hg can be said to "slip" from their mercuric atom (the radioactive mercuric atom), with R and X simultaneously "slipping" from the radioactive mercuric atom (formerly belonging to the molecule R_2Hg[11]).

In the case of such a "slipping" the transition state appears to be represented by a bipyramidal complex such as:



with IV - a free radical chain mechanism and V the isotope exchange in the presence of equilibrium

$$2RHgX \rightleftharpoons R_2Hg + HgX_2$$

for example

$$(a)\ 2RH\overset{*}{g}X \rightleftharpoons R_2H\overset{*}{g} + H\overset{*}{g}X_2$$

$$(b)\ R_2Hg + H\overset{*}{g}X_2 \rightleftharpoons RH\overset{*}{g}X + RHgX$$

Scheme I is in agreement with our experimental data, Schemes II to V are not.

The reaction does not involve free radicals as kinetically independent particles (Scheme IV), the stereochemical configuration being thereby fully retained. Had the reaction followed Scheme III it would not have resulted in distribution of optical activity between RHgX and R_2Hg. The considerations below indicate that the isotope exchange in question proceeds with no equilibrium (Scheme Va) or with parallel reactions (Schemes II and III).

---

[11] A simpler case of concurrent "slipping" of two radicals from one mercuric atom to another in the reaction $R_2Hg + {}^{203}Hg \rightleftharpoons R_2{}^{203}Hg + Hg$ can be considered as proven.[3]

The isotope exchange thus obeys the equation.

$$-\ln (1-F) = \frac{A + B}{AB} Vt \qquad (1)$$

where F denotes the extent of exchange, A and B the concentration of starting substances, V the exchange rate constant and t the time.

Redistribution of optically active radicals in the reaction

$$R_2Hg + \overset{*}{R}HgX \rightleftharpoons \overset{*}{R}HgR + RHgX$$

with $\overset{*}{R}$ being an optically active radical, is in some way similar to isotope exchange. The radicals being chemically identical leads to the establishment at some particular moment of equilibrium that is characterized by RHgX containing 1/3 of the original amount of optically active radicals, with dialkylmercury accounting for the remaining 2/3; following this redistribution continues at the same rate but now in the condition of "optical equilibrium".

Hence, for the radical exchange process one can also write an equation expressing the exponential dependences of the extent of exchange on time such as

$$-\ln (1-F) = \frac{2A + B}{2AB} V't \qquad (2)$$

where F' is the extent of radical exchange, $F' = (\alpha_t)/(\alpha_\infty)$ with α_t and α_∞ denoting the angles of RHgX before and after equilibrium is reached; A is the concentration of R_2Hg that is doubled due to there being two radicals; B is the concentration of RHgX; V' is the constant exchange rate and t is the time.

Fig. 1. (curve II) shows the exponential dependence of the magnitude of exchange of optically active radicals on time determined experimentally (run 2).

The increase in isotope exchange is shown here (curve I) as well as in Table 3.

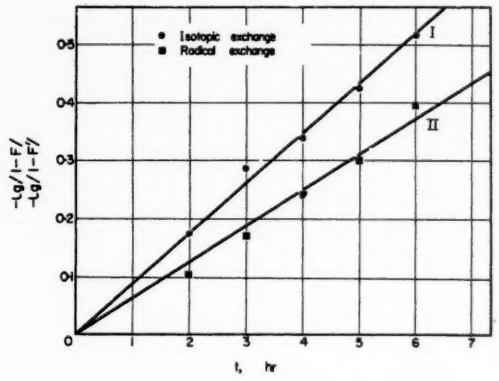


FIG. 1.

TABLE 3

Run 2: Increase in Isotope Exchange

Time (hr)	2	3	4	5	6
Isotope exchange (%)	33.0	48.5	54.0	65.0	69.5
- ln (1 - F)	0.174	0.287	0.338	0.426	0.516
$V.10^3$ mole/l.hr	5.00	5.50	4.85	4.90	4.95
$V.10^3$ (average)		5.0±0.2			

It is evident that according to Scheme I the exchange between mercury and radicals should take place in one step:

$$\overset{*}{R}{}^{203}Hg \vdots X + R \vdots HgR \rightleftharpoons \overset{*}{R}{}^{203}HgR + RHgX$$

$$\text{or } \overset{*}{R}Hg \vdots R + R^{203}Hg \vdots X \rightleftharpoons R^{203}HgR + \overset{*}{R}HgX$$

Hence the exchange rates V and V' from equations (1) and (2) can be taken as equal, V=V'.

If, to some extent, exchange of R and R (Scheme II) and not only exchange of R and X had caused the reaction, the radical exchange rate should have

exceeded that of the isotope exchange of mercuric atoms ($V' > V$). If the reaction had been at least partly affected by the mechanism of slipping (Scheme III), V should be greater than V'. It is also highly unlikely that the reaction might proceed simultaneously following Schemes I and II with these different processes running at equal rate. In the case of Scheme V

$$2R^{*203}HgX \rightleftharpoons R^{*}_{2}{}^{203}Hg + {}^{203}HgX_2$$

$$R_2Hg + {}^{203}HgX_2 \rightleftharpoons RHgX + R^{203}HgX$$

each mercuric atom exchange must be accompanied by that of two optically active radicals (i.e. $V' > V$)

$$2R^{*203}HgX + R_2Hg \rightleftharpoons R^{*}_{2}{}^{203}Hg + R^{203}HgX + RHgX$$

Our experiments have shown $V = V'$ (see Tables 2 and 3), within the limits of the experimental error. The reaction has thus been proved to follow Scheme 1 only.

Bearing in mind that $V = V'$, it is possible to write an equation to include both the magnitude of isotope exchange F and the radical exchange F'. For (1) and (2) one then obtains:

$$\ln (1 - F') = \frac{2A + B}{2(A + B)} \ln (1 - F) \qquad (3)$$

In Table 4 are given the angles of rotation (α_{R_2Hg}) calculated from the magnitude of isotope exchange in terms of equation (3) with deviations from the experimental value not exceeding 2.5 per cent.

To come to a definite conclusion with regard to the transition state in the reaction in question it is necessary to have some additional, primarily kinetic evidence, which is at present being accumulated.

1960

TABLE 4

Comparative Data for the Measured Angles of Rotation and Angles Calculated from Isotope Exchange

Time (hr)	3[a]	5[a]	2	3	4	5	6
Measured α R_2Hg	-7.6°	-8.11°	-28.8°	-27.6°	-26.6°	-25.8°	-24.8°
Calculated α R_2Hg	-7.6°	-8.3°	-28.3°	-27.0°	-26.4°	-25.6°	-24.9°
Relative deviation (%)	0	2.5	1.8	2.2	0.8	0.8	0.4

[a] The data are taken from run 1, others from run 2.

Tetrahedron Letters No. 19, pp. 16-20. 1960. Pergamon Press Ltd. Printed in Great Britain

OXYGEN HETEROCYCLES[1]

THE STRUCTURE OF THE ISOFLAVANONE SOPHOROL

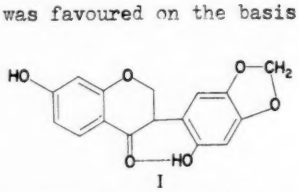
Hiroshi Suginome

Department of Chemistry, Faculty of Science,

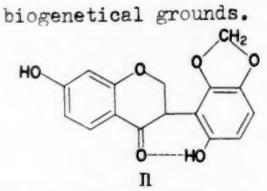
Hokkaido University, Sapporo, Japan

(Received 13 July 1960)

IN a previous paper[2] it was shown that the structure of sophorol, a new isoflavanone from the heartwood of Maakia amurensis Rupr. et Maxim. var. Buergeri (Maxim.) C. K. Schneid,* was either 2',7-dihydroxy-4',5'-methylenedioxyisoflavanone (I) or 2',7-dihydroxy-5',6'methylenedioxyisoflavanone (II). The former was favoured on the basis of biogenetical grounds.



I



II

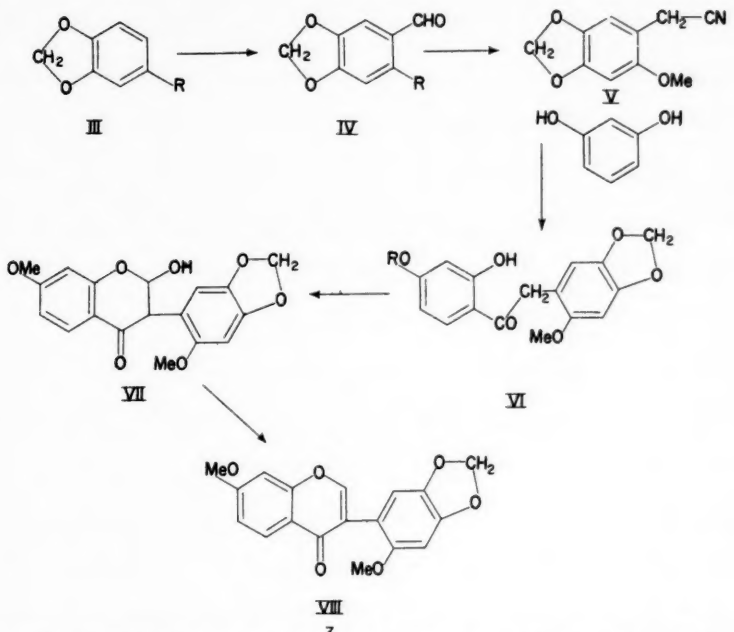
The structure of sophorol has now been confirmed to be (I) by the syntheses of hydrolysed product (VI) R = CH_3 and palladium dehydrogenation product (VIII) of O-dimethylsophorol, as follows:

---

* Leaguminoceae. The plant material used in this work had been originally considered as Sophora japonica, L.

[1] Previous paper in this series: Hiroshi Suginome and Tsukasa Iwadare, Bull.Chem.Soc. Japan 33, 567 (1960).

[2] Hiroshi Suginome, J.Org.Chem. 24, 1655 (1959).



III IV V VI VII VIII

The earlier preparative method[3] of starting 2-hydroxy-4,5-methylene-dioxybenzaldehyde (which is also an important building stone for the synthesis of some naturally occurring oxygen heterocycles, ayapin,[4] pachyrrhizon,[5] pachyrrhizin,[6] and jamaicin[7]) was rather laborious and therefore unsatisfactory.

By a revised preparation, sesamol[8] (III) R=OH, which was prepared by Baeyer-Villiger oxidation of piperonal (III) R = CHO, was formylated by

---

[3] K.N. Campbell, P.F. Hopper and B.K. Campbell, J.Org.Chem. 16, 1736 (1951).

[4] E. Späth, P.K. Bose and J. Schläger, Ber. 70, 702 (1937).

[5] H. Bickel and H. Schmid, Helv.Chim.Acta 36, 664 (1953).

[6] E. Simonitsch, H. Forei and H. Schmid, Monatsh. 88, 541 (1957); P. Rajagopalan and A.I. Kosak, Tetrahedron Letters No. 21, 5 (1959).

[7] O.A. Stamm, H. Schmid and J. Büchi, Helv.Chim.Acta 41, 2006 (1958).

[8] J. Boeseken, W.D. Cohen and C.J. Kip, Rec.Trav.Chim. 55, 815 (1936). M. Beroza, J.Agr.Food.Chem. 4, 49 (1956).

Gattermann procedure, yielding (IV) R = H in high yield.

Methylated aldehyde (IV) R = CH_3 was converted into the corresponding substituted phenylacetonitrile (V) (m.p. 123-124°. Found: C, 63.10; H, 5.00; N, 7.18. $C_{10}H_9O_3N$ requires: C, 62.82; H, 4.75; N, 7.33%) I.R.-C≡N[9] 2241 cm^{-1} U.V. spectrum: λ_{max} (ethanol) 213, 239 and 301 mμ (ε; 4741, 5540 and 6946) through the corresponding azlactone (m.p. 260°. Found: C, 66.95; H, 4.27. $C_{18}H_{13}O_5N$ requires: C, 66.87: H, 4.05%). This was condensed with resorcinol into a desoxybenzoin derivative (VI) R = H (m.p. 164-165°. Found: C, 63.29; H, 4.50. $C_{16}H_{14}O_6$ requires: C, 63.57; H, 4.67%) under Hoesch condition using mixed solvent of chloroform-ether.

This, on partial methylation by ethereal diazomethane, gave 2-hydroxy-, 4,2'-dimethoxy-4,5-methylenedioxydesoxybenzoin (VI) R = CH_3 (m.p. 131-132°. Found: C, 64.50; H, 5.07. $C_{17}H_{16}O_6$ requires: C, 64.55; H, 5.10%) identical with a specimen derived from the natural product as shown by the I.R. spectra and mixed melting point determination. This desoxybenzoin (VI) R = CH_3 was converted into 2',7-dimethoxy-4',5'-methylenedioxyisoflavone (VIII) m.p. 208-209°. (C, 65.98: H, 4.20. $C_{18}H_{14}O_6$ requires: C, 66.25; H, 4.32%) through the corresponding intermediary 2-hydroxyisoflavanone (VII) (m.p. 185°. Found: C, 62.60; H, 4.80. $C_{18}H_{16}O_7$ requires: C, 62.79; H, 4.68%) I.R. -CO. 1657 cm^{-1} OH. 3400 cm^{-1}. This isoflavone was identical with dehydro-O-dimethyl sophorol[2] (mixed melting point and I.R. spectra), thus confirming the structure (I) for sophorol.

The biogenesis of the flavonoids and the related compounds has already

---

[9] R. E. Kitson and N. E. Griffith, Analyt. Chem. 24, 334 (1952).

1960

been discussed extensively.[10,11]

The occurrence of sophorol is of importance in view of the biogenesis of complex naturally occurring oxygen heterocycles namely, group A (rotenoids[12a,13]: rotenone, sumatrol, deguelin, toxicarol, tephrosin, elliptone,[12b] malaccol[12c] and pachyrrhizon[5]) and group B (chromanocoumarane or coumarinocoumarone ring systems: pterocarpin, homopterocarpin,[14] coumoestrol,[15] pachyrrhizin,[6] erosnin,[16] and wedelolactone[17]), derived from 3-phenylchroman system.

As pointed out previously[2] sophorol possesses essential core and oxygenation pattern of rotenoids.

Argument[7,11,13] seems to be justified that in rotenoids, the isoflavone or isoflavanone ring systems were initially constructed and formaldehyde unit could be introduced at a later stage.*

As Birch has noted,[18] the known occurrence of 2'-oxygenated flavonoids

---

* See "Note added in proof" on p. 20.

10 R. Robinson, The Structural Relations of Natural Products p. 43. Clarendon Press (1955); T.R. Seshadri, Ann. Rev. Biochem. 20, 487 (1951); T.A. Geissman and Hinreiner, Botan. Rev. 18, 77 (1952).

11 T.R. Seshadri, Tetrahedron 6, 169 (1959).

12a,b R.D. Haworth, Ann. Rep. Chem. Soc. 346 (1937); Ibid. 311 (1938); S. H. Harper, J. Chem. Soc. 1424 (1939); c S.H. Harper, J. Chem. Soc. 309 (1940).

13 H.A. Offe, Angew. Chem. 60, 9 (1948).

14 A. McGookin, A. Robertson and W.B. Whalley, J. Chem. Soc. 787 (1940); E. Späth and J. Schläger, Ber. 73, 1 (1940).

15 O.H. Emerson and E.M. Bickoff, J. Amer. Chem. Soc. 80, 438 (1958).

16 J. Eisenbeiss and H. Schmid, Helv. Chim. Acta 61 (1959).

17 T.R. Govindachari, K. Nagarajan, B.R. Pai and P.C. Parthasarathy, J. Chem. Soc. 545 (1957).

18 A.J. Birch in L. Zechmeister's, Progress in the Chemistry of Organic Natural Products Vol. 14, p. 186. Springer, Vienna (1957).

had been comparatively rare. However, recent survey of plant material, particularly rotenone bearing leaguminous (fabaceous) plant, has showed a possibility of wide distribution of new 2'-oxygenated isoflavonoids.

These are mundulone,[19] tlatlancuayin,[20] ferreirin, homoferreirin,[21] jamaicin,*[7] toxicarol isoflavone[22] and munetone.[23] Among them, structural similarity of sophorol with jamaicin is of particular interest. Jamaicin is a corresponding isoflavone bearing one isoprene unit on 8-position of sophorol.

Furthermore, it may be mentioned in general that 2'-oxygenated isoflavanoids and above-mentioned group B compounds has also a possible biogenetic interrelationship, which King and Neill originally suggested[21] with respect to the pterocarpin-ferreirin link. Based on this consideration the synthesis of the pterocarpin ring system was recently accomplished[1] by the present authors.

A more detailed description of this work will be published shortly.

Acknowledgments - The author is grateful to Professors Toshi Irie, Takeshi Matsumoto and Tadashi Masamune for their encouragement while this investigation was in progress. Author's thanks is also due to Mr. M. Kusama for the preparation of starting materials.

Note added in proof: The structure determination and synthesis of munduserone, a "missing link" between rotenoids and simple 2'-hydroxy isoflavanoids, were very recently reported. [N. Finch and W.D. Ollis, Proc. Chem. Soc. 176 (1960); J.R. Herbert, W.D. Ollis and R.C. Russell, Ibid. 177 (1960)].

* The writer thanks Dr. W. D. Ollis of The University Bristol for drawing his attention to this example.

19 B.F. Burrows, N. Finch, W.D. Ollis and I.O. Sutherland, Proc. Chem. Soc. 150 (1959).

20 P. Crabbé, P.R. Leeming and C. Djerassi, J. Amer. Chem. Soc. 80, 5258 (1958).

21 F.E. King and K.G. Neill, J. Chem. Soc. 4752 (1952).

22 S.H. Harper, J. Chem. Soc. 1178 (1940); Ibid. 595 (1942).

23 N.L. Datta, J. Indian Chem. Soc. 36, 165 (1959).

Tetrahedron Letters No. 19, pp. 21-24, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

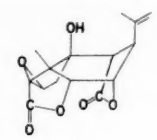
THE MOLECULAR STRUCTURE AND ABSOLUTE CONFIGURATION OF PICROTOXININ

B. M. Craven

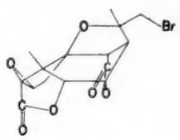
The Crystallography Laboratory, University of Pittsburgh, Pittsburgh 13, Pennsylvania

(Received 17 July 1960)

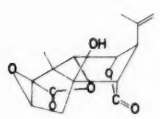
THE structure (Ia) proposed for picrotoxinin ($C_{15}H_{16}O_6$) by Conroy[1,2] and supported by his conformational analysis has now been confirmed by the crystal structure analysis of a bromo derivative ($C_{15}H_{15}O_6Br$) using the methods of X-ray diffraction. Crystals of α-bromopicrotoxinin, for which



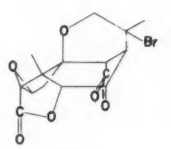
Ia



IIa



Ib



IIb

---

[1] H. Conroy, J. Amer. Chem. Soc. 73, 1889 (1951).

[2] H. Conroy, J. Amer. Chem. Soc. 89, 5550 (1957).

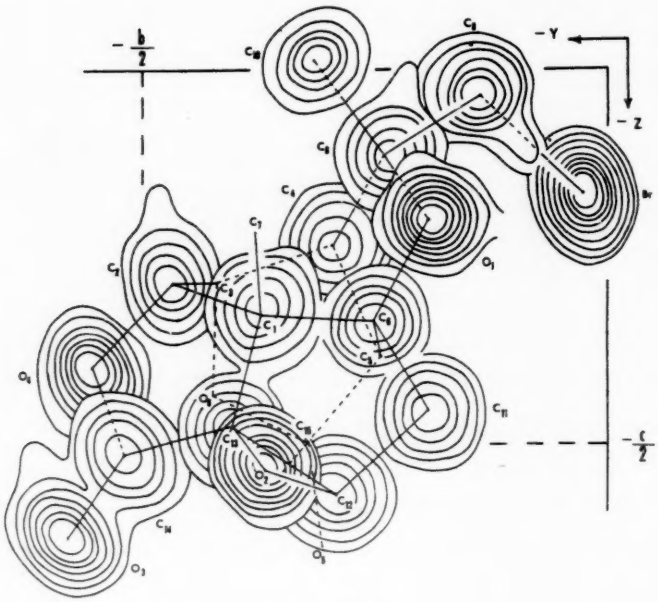


FIG. 1(a).

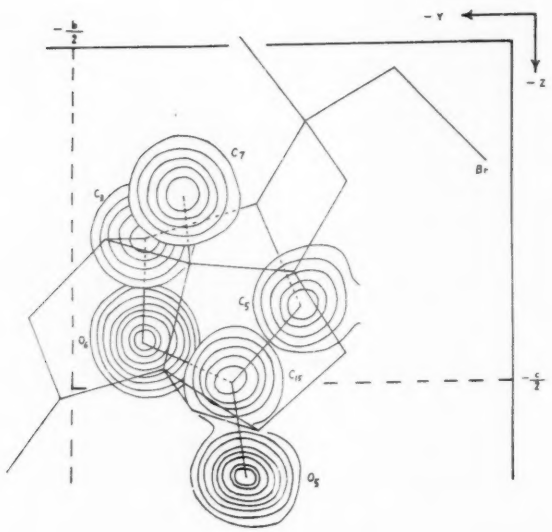


FIG. 1(b).

1960

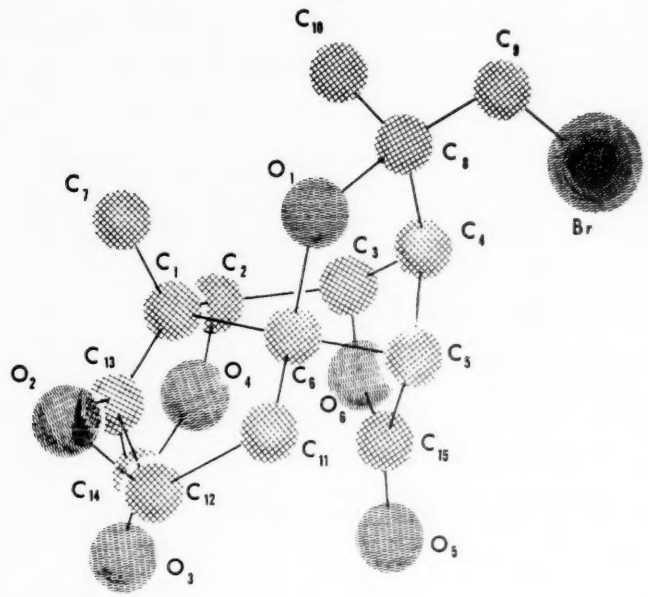


FIG. 2.

the structures (IIa) or (IIb) were proposed by Conroy have been shown to be a mixture of two crystalline modifications,[3] here called α_1 and α_2. The relationship between these is still unknown. The final electron density distribution calculated in the three-dimensional crystal structure analysis of α_1 - bromopicrotoxinin is represented in Fig. 1(a) and (b) in which the atomic labeling is that of Conroy. The corresponding molecular structure which is shown in Fig. 2 is the mirror image of the structure (IIa) as it appears in Conroy's papers. No chemical evidence has yet been advanced as to which of the two enantiomorphs represented in II(a) and Fig. 2, is the true configuration. The evidence of anomalous X-ray scattering has been

---

[3] B. M. Craven, Acta Cryst. 12, 254 (1958).

examined according to the methods of Bijvoet et al.[4] and this shows the true molecular configuration to be that of Fig. 2.

It follows that the true configuration of picrotoxinin itself is (Ib), which is also the mirror image of the structure as it appears in Conroy's papers.

It is an important feature of Conroy's conformational analysis of picrotoxinin that there should be steric hindrance to a rearward nucleophilic attack at the epoxide ring ($C_{12}O_2C_{13}$). From the crystal structure studies, the two lactone bridges C_5 to C_3 and C_{13} to C_2 indeed are found to form a protective "cage" behind the epoxide ring, some of the cage dimensions being, - C_{12} - O_5, 3.29 Å; C_{12} - C_{15}, 3.18 Å; C_{13} - C_{15}, 3.11 Å; C_{14} - C_{15}, 3.34 Å.

The detailed results of the X-ray analysis are being prepared for publication.

This research has been supported by Grant No. G-9971, from the National Science Foundation.

---

[4] J. M. Bijvoet, A. F. Peerdemann and A. J. van Bommel, Nature, Lond. 168, 271 (1951).

Tetrahedron Letters No. 19, pp. 25-29, 1960. Pergamon Press Ltd. Printed in Great Britain

THE STRUCTURE OF NEORUSCOGENIN

L. Mandell

Department of Chemistry, Emory University, Atlanta, Georgia

A. L. Nussbaum and E. P. Oliveto

Natural Products Department, Schering Corporation, Bloomfield, N.J.

(Received 8 July 1960)

A recent communication from France[1] presents convincing infrared and chemical evidence that one of the sapogenins isolated from Ruscus aculeatus L., neoruscogenin, differs from ruscogenin, a companion substance, by possessing an additional double bond exocylic to ring F. Since the former had been described as simply the C-25 epimer of the latter[2] by the discoverers of these sapogenins, and since other workers [3,4] in the field implicitly accepted that assignment, we should like to submit the following physical evidence which bears out the more recent structure.

---

1 J. Robert, R. Vaupré and G. Poiget, Compt. rend. 3187 (1960).

2 C. Sannié and H. Lapin, Bull. soc. chim. 1237(1957).

3 D. Burn, B. Ellis and V. Petrow, J. Chem.Soc. 795 (1958).

4 A. L. Nussbaum, F.E. Carlon, D. Gould, E.P. Oliveto, E.B. Hershberg, M.L. Gilmore and W. Charney, J. Amer. Chem. Soc. 81, 5230 (1959)

A comparison (Table I) of the nuclear magnetic resonance spectra (fig. 1) of the diacetates of ruscogenin and neoruscogenin clearly shows (a) the appearance of a distinct new band in the vinylic proton region for neoruscogenin diacetate, (b) shift of a peak assigned to the C_{27}-protons adjacent to oxygen in ring F [5] in that sapogenin, as compared to ruscogenin diacetate, and (c) the absence of a band in neoruscogenin diacetate assigned to the C_{26}-protons in ruscogenin diacetate. These observations find a ready explanation in the proposed new structure[1].

Ruscogenin has been converted to the corresponding $\Delta^{1,4}$-dien-one, and the latter was shown to be identical[4] with the dehydrogenation product from diosgenone, $\Delta^{1,4}$-20α, 22β, 25 D-spirostadien-3-one [6]. On the other hand, Burn, Ellis and Petrow [3] carried out a like series of reactions on a presumed 1:1 mixture of ruscogenin and neoruscogenin but did not isolate the 25 D isomer ascribable to ruscogenin.

---

[5] Private communication from Dr. J.F. Shoolery, Varian Associates. We should like to thank Dr. Shoolery for an enlightening discussion of the NMR spectrum of ruscogenin diacetate which he kindly measured for us some three years ago.

[6] For sapogenin nomenclature, see ref. 8.

1960

TABLE I

Comparison of Corresponding NMR Bands of the Diacetates of Ruscogenin and Neoruscogenin

Rusco	Neorusco	Assignment	Comment
63	70.5	Proton at C_6	7
-	100.0	Δ 25(27)	Not present in Rusco
105 (low multiplet)	110	C_1, C_3, C_{16} [8]	
	122.5 132.0 144.0	C_{26}	Note shift
150	-	C_{26}	
209	209.5	Acetate Me protons	
226	-	C_{27} Me	Not present in Neorusco
244	243.5	C_{19}	9
259	258	C_{18}	

[7] This signal accurs at a rather low field as compared to a large number of Δ^5-steroids; see J.N. Shoolery and M.T. Rogers, J. Amer. Chem. Soc. 80, 5121 (1958). It is believed to be caused by an effect the 1β-acetyl substituent has on the normal polarization of the Δ^5 double bond. This effect will be discussed elsewhere.

[8] The proton at C_{16} is assigned to this peak, in addition to the protons of the two carbons substituted by equatorial acetates, as the result of peak area measurements and comparison of these spectra with those of diosgenin acetate, 1β,3β-diacetoxy-Δ^5-pregnen-20-one, and pregnenolone acetate.

[9] This represents a small shift from the normal position for C_{19}-angular methyl which is thought to be cause again by the proximity of the 1β-acetate (see previous ref.) Incidentally, this confirms the stereochemistry already proved by chemical means by W.R. Benn, F. Colton and R. Pappo, J. Amer. Chem. Soc. 79, 3920 (1957).

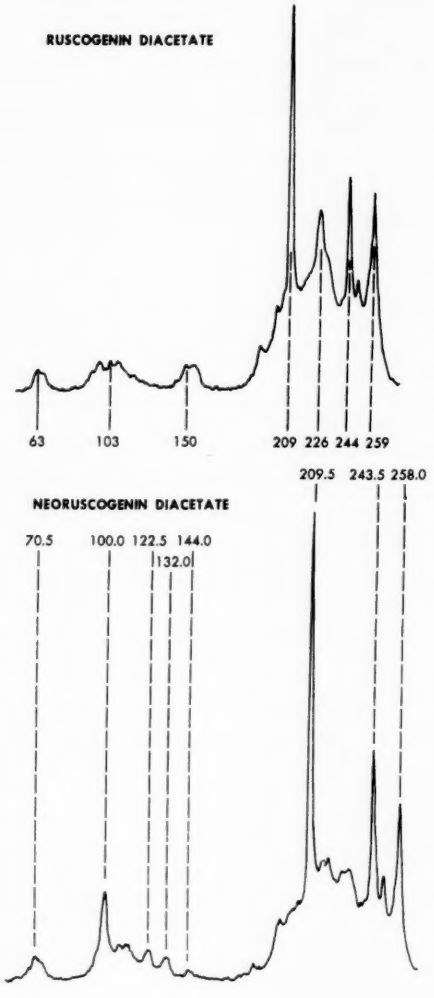


Fig 1

NMR Spectra of the Diacetates of Ruscogenin and Neoruscogenin.

The spectra were measured in deuterochloroform solution. A chloroform capillary is used as arbitrary reference zero. Signal at 40 mega-cycles/sec., chemical shift in cycles/sec.

1960

They concluded that they had in hand $\Delta^{1,4}$-20α, 22β, 25 L-spirostadien-3-one, the corresponding "normal" isomer derived from neoruscogenin. If their premise is correct, this structure should now be changed to $\Delta^{1,4,25(27)}$-20α, 22β-spirostatrien-3-one.

Both the English authors [3] and the Schering group [4] had observed that neoruscogenin underwent the Marker pseudo-reaction more readily than did ruscogenin. This was ascribed [10] to steric decompression as discussed by Wall and Serota [11]. It is clear that this driving force can be only partly operative in the case at hand.

---

10 See footnote 21, ref. 4

11 M. E. Wall and S. Serota, J. Amer.Chem.Soc. 79, 6481 (1957).

Tetrahedron Letters No. 19, pp. 30-35, 1960. Pergamon Press Ltd. Printed in Great Britain.

A BIOGENETICALLY-PATTERNED LABORATORY SYNTHESIS IN THE STRYCHNINE - CURARE ALKALOID SERIES

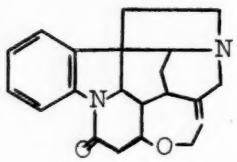
E. E. van Tamelen, L. J. Dolby and R. G. Lawton

Department of Chemistry, University of Wisconsin,

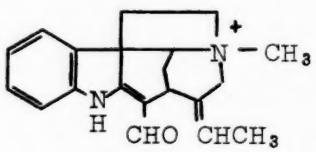
Madison, Wisconsin

(Received 15 July 1960)

Although the method by which Nature constructs the complex polycyclic structures characteristic of strychnine (I) and related



I



II

bases (including the curare alkaloid group e.g. C-fluorocurarine, II[1,2]) has been the subject of detailed discussion,[3,4] no synthesis

---

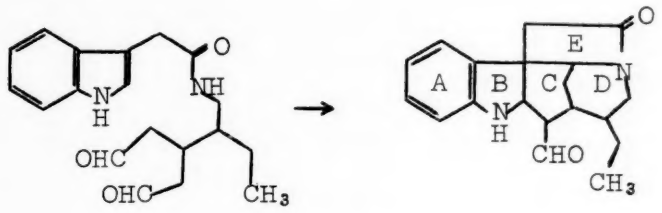
[1] W. von Philipsborn, H. Meyer, H. Schmid and P. Karrer, Helv. Chim. Acta 41, 1257 (1958).

[2] H. Fritz, E. Besch and T. Wieland, Angew. Chem. 71, 126 (1959).

[3] R. B. Woodward, Nature 162, 155 (1948).

[4] E. Wenkert and N. V. Bringi, J. Am. Chem. Soc. 81, 1474 (1959).

simulating a reasonable biogenetic route has been realized in the laboratory. We have discovered that the simple indole derivative III under mild conditions directly generates the fused system IV



III IV

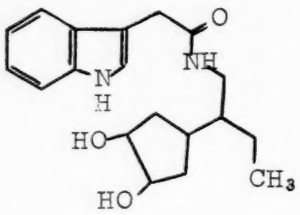
containing five rings and six asymmetric centers, and duplicating the essential framework of the strychnine-type natural products.[5]

The intermediary, unisolated dialdehyde was produced by periodate cleavage of the diol V, obtained by the following series of operations. The p-toluenesulfonate of Δ^3-cyclopentenol (prepared by hydroboration-oxidation of cyclopentadiene)[6] was used to alkylate ethylcyanoacetic ester, and the resulting product (b.p. 138-140°/ 13 mm.) was saponified and decarboxylated to give the unsaturated nitrile

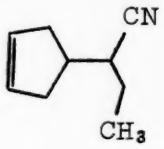
---

[5] For the total synthesis of strychnine, see R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. U. Daeniker and K. Schenker, ibid. 76, 4749 (1954).

[6] E. L. Allred, J. Sonneberg and S. Winstein, ibid. 81, 5833 (1959).

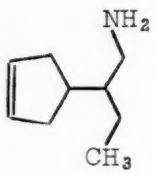


V

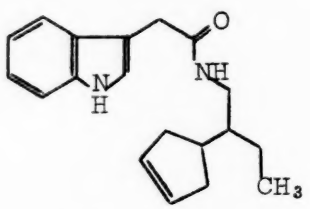


VI

(VI) (b.p. 115°/30 mm.). The primary amine (VII) (b.p. 97-100°/30 mm.) obtained by lithium aluminum hydride reduction of VI was heated with methyl indole-3-acetate, providing the oily amide VIII.

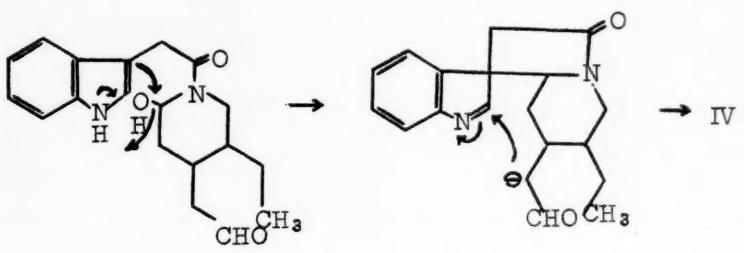


VII



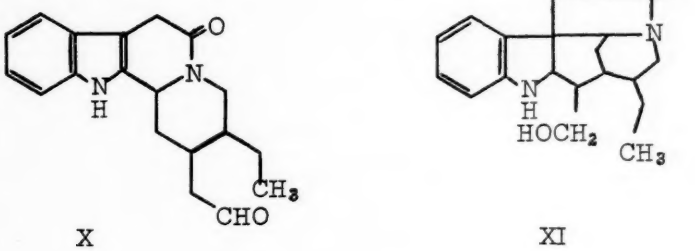
VIII

Hydroxylation of crude VIII by means of osmium tetraoxide led to the required diol V, characterized as the trinitrobenzene complex, m.p. 145.5-146.5°. When generated, intermediate III cyclizes spontaneously to the alkanol amide IXa, detected by its infrared spectrum (peaks at 5.79 and 6.03 μ). On being heated briefly in aqueous acetic acid-sodium acetate or formic acid-sodium formate, III-IXa, by-passing



IXa IXb

normal α-cyclization to X, forms directly the indoline IV, presumably by way of sequence IXa → IXb → IV.[7] The unstable aldehyde lactam (not analyzed), appearing in part as the N-formyl derivative,



X XI

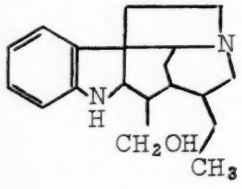
was reduced with sodium borohydride to the lactam alcohol XI (m.p. 53-56°, sublimed at 145°/ca. 10^{-4} mm.; picrate, m.p. 152-154°), which in turn was converted with lithium aluminum hydride to

---

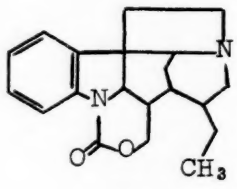
[7] The factors controlling the course of cyclization in this and related cases are under investigation in this Laboratory.

the amino alcohol XII (sublimed at 110°/ca. 10^{-4} mm.).

Assignment of structure to product IV depends upon the following observations. The ultraviolet spectrum of, e.g., XI (λ_{max}^{alc} 243, 295 mu, ϵ = 9600, 3400) is virtually identical with that of the Wieland-Gumlich aldehyde (λ_{max}^{alc} 243, 295 mu, ϵ = 9100, 3000)[8] thus revealing the presence of the indoline ring system (ring A and saturated ring B). Substance IV or XI possesses a lactam carbonyl band in the infrared at 5.97 μ, indicating a five-membered E-ring.[9] The presence of the second new carbon-carbon bond, incorporated into a β-aminoaldehyde system and requiring the presence of a six-membered C-ring, was proved by conversion of alcohol XII to a tetrahydrooxazinone (XIII), m.p. 123-126° (infrared



XII



XIII

[8] F. E. Bader, E. Schlittler, and H. Schwarz, Helv. Chim. Acta 36, 1258 (1953).

[9] P. J. Scheuer, J. Am. Chem. Soc. 82, 193 (1960).

peak at 5.97 μ). This heterocyclic derivative was secured by reaction with phenylchlorocarbonate, followed by cyclization of the intermediary urethane (carbonyl peak at 5.90 μ) with sodium hydride in benzene.[10] Finally, elemental analyses demonstrate that complete cyclization of III is accompanied by dehydration. These findings allow no reasonable structure other than that proposed for the cyclization product IV.

Where possible and except as indicated, elemental analyses have been obtained on all substances described.

This research was supported by a National Science Foundation postdoctoral fellowship (to L. J. D.).

---

[10] In a model series, N-phenyl-3-aminopropanol was converted similarly to the phenyl carbamate (5.90 μ), and thence to the cyclic urethane (5.97 μ).

Tetrahedron Letters No. 19, pp. 36-42, 1960. Pergamon Press Ltd. Printed in Great Britain

ECHITAMINE

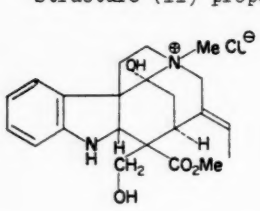
A. J. Birch, H. F. Hodson, B. Moore, H. Potts,

and G. F. Smith

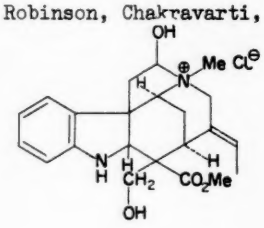
Department of Chemistry, University of Manchester

(Received 29 June 1960)

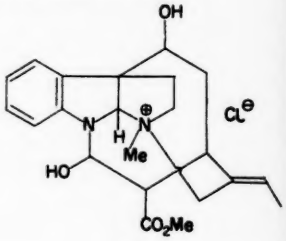
RECENT months have seen the proposal of three different structures for the alkaloid echitamine chloride: structure (I), proposed by Conroy et al.,[1] structure (II) proposed by Robinson, Chakravarti, Chakravarti and Ghose,[2]



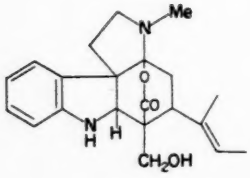
I



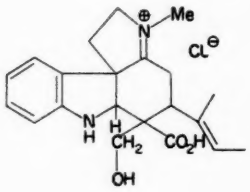
II



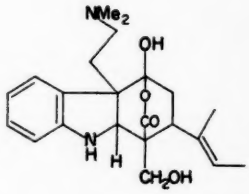
III



IV



VI



V

[1] H. Conroy, R. Bernasconi, P.R. Brook, R. Ikan, R. Kurtz and K.W. Robinson, Tetrahedron Letters No. 6, 1 (1960).

[2] D. Chakravarti, R.N. Chakravarti, R. Ghose and Sir Robert Robinson, Tetrahedron Letters No. 10, 10 (1960); Ibid. No. 11, 25 (1960).

and structure (III), proposed by Chatterjee, Ghosal and Ghosh Majundar.[3]

We wish in this communication to look at each of these structures critically in the light of the available evidence.

Structure (I) goes a long way towards interpreting the known reactions of the alkaloid, but fails on one important point. The Hofmann degradation of echitinolide (IV) should, on the basis of Conroy's formulation, lead to the unique structure (V) for the methine. This methine is described by Govindachari and Rajappa[4] as a base showing λ_{max} 245, 307 mμ (log ε 3.94, 3.54) in ethanol, changing to 240, 297 mμ (log ε 3.90, 3.49) on acidification. We have also studied the Hofmann degradation of echitinolide, but have found that the immediate product of the reaction is an as yet amorphous base $C_{22}H_{30}O_4N_2$ (base A), which has a C = O stretching frequency of 1740 cm^{-1}, OH-3630 cm^{-1}, NH-3455 cm^{-1} and which has λ_{max} 240, 296 mμ (ε 7450, 2820) unchanged on acidification; this base A is converted by being passed over alkaline alumina in benzene into a crystalline isomeric base B, m.p. 169-173°, which has a C = O stretching frequency of 1723 cm^{-1}, OH-3590 cm^{-1}, NH-3470 cm^{-1} and λ_{max} 247, 306 mμ (ε 9100, 3640) changed to 243, 302 mμ (ε 9200, 3550) on acidification. It is not possible to account for the production of two isomeric methines on the basis of structure (V). That the double bond of the isobutenyl group is not involved in this isomerization is shown by the fact that β-dihydroechitinolide undergoes the Hofmann degradation to give a completely analogous pair of methine bases (catalytic hydrogenation of echitinolide in glacial acetic acid gives two isomeric

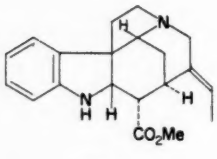
---

[3] A. Chatterjee, S. Ghosal and S. Ghosh Majundar, Chem. & Ind. 265 (1960).

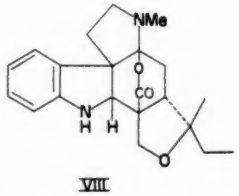
[4] T.R. Govindachari and S. Rajappa, Chem. & Ind. 1549 (1959).

dihydro derivatives whose I.R. spectra are identical: α-, with m.p. 120-124° partially recrystallizing to melt finally at 195-197°, β-, with m.p. 92-97° partially recrystallizing to melt finally at 112-117°.

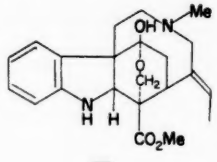
The following are further criticisms of structure (I) proposed by Conroy et al.: (a) The American authors believe the failure of N(a) in (I), (IV), and (V) to protonate in acid solution to be due to steric hindrance of the N(a) ammonium ion to solvation. We should like to point out that in 2,16-dihydroakuammicine (VII), in which there is the same order of steric hindrance around N(a), protonation of N(a) is complete in 0.5 N ethanolic HCL.[5] It is noteworthy that (i) neither echitamine chloride nor echitinolide



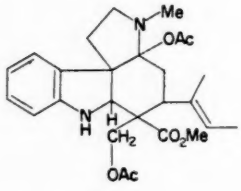
VII



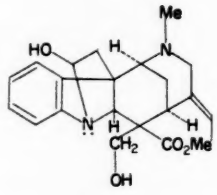
VIII



IX



X



XI

are protonated on N(a) even in concentrated hydrochloric acid and (ii) acetic anhydride and sodium acetate at the b.p. acetylate echitinolide cleanly on N(a).

---

[5] P.N. Edwards and G.F. Smith, In press.

1960

(b) The U.V. spectrum of echitinolide (IV) undergoes a marked hypsochromic shift on acidification. This is accounted for by Conroy in terms of conversion of (IV) into an immonium carboxylic acid (VI), the spectral shift being held to be due to a conformational change caused by the opening of the lactone ring and involving N(a). We have hydrogenated diacetyl echitamine chloride to a di-O-acetyl base, $C_{26}H_{34}O_6N_2$, in which the carbomethoxy group is still present (Found: OMe, 6.15. Calc. for one OMe in $C_{26}H_{34}O_6N_2$, 6.6%). This base dissolves in 0.5 N aqueous HCl at room temperature and can be recovered unchanged on basification; it is hydrolysed to echtinolide by dilute methanolic sodium hydroxide at the boiling point. This diacetyl carbomethoxy base, which on Conroy's formulation should have structure (X), has λ_{max} 251, 308 (ε 7000, 2800), changed to 241, 297 mμ (ε 7500, 2800) on acidification. Since this base cannot undergo a reversible change of conformation of the type postulated by Conroy, the latter's argument concerning the spectral shift is invalidated. A further weakness of the lactone ring-opening hypothesis is that it fails to account for the resistance of echitinolide to reduction in acid solution, for the immonium ion in (VI) is not particularly sterically hindered (questions of steric hindrance were decided on by inspection of Stuart - Briegleb models). We feel that the Ø-N-C-N system still affords the simplest rationalization of the data,[6] though any system which brings a positively charged N(b) spatially very close to N(a) will give rise to the same effects. The observation that a 9 mμ hypsochromic

---

[6] A.J. Birch, H.F. Hodson and G.F. Smith, Résumé des Communications, Tome II, p. 207, XVIth Internat. Congr. Pure. Appl. Chem., Paris, 1957; Proc. Chem. Soc. 224 (1959); T.R. Govindachari and S. Rajappa, Ibid. 134 (1959).

shift of the acylarylamine type spectrum of O,N-diacetyl echitinolide occurs on acidification tends to support this.

(c) We have found both echitinolide and isoechitinolide not to be reduced by lithium aluminium hydride in ether at room temperature and only slowly at the boiling point. This would seem to indicate very considerable steric hindrance to approach of the reagent to the carbonyl carbon. This is not at all evident in (IV), and even less so in isoechitinolide, formulated by Conroy as (VIII). [We have found isoechitinolide to crystallize from ether as plates, m.p. 182-184° (cf. m.p. 149-154° quoted in reference 1)].

(d) Echitamine base, which we have also and independently obtained in the form of a crystalline benzene solvate, does not give any trace of acetaldehyde on ozonolysis in CCl_4, but gives formaldehyde in 40% yield. This is not easily reconcilable with structure (IX). We also differ from the American authors on the question of the speed with which echitamine reverts to echitamine hydroxide (I, OH^- instead of Cl^-): we find this conversion to occur very rapidly, for we observe echitamine to dissolve in water to give a solution the pH of which rises in less than one minute to a value correspondong to complete ionization as the quaternary hydroxide. We are of the opinion that the U.V. spectrum of (II) cannot be measured in ethanol, the spectrum observed being that of the quaternary hydroxide. The U.V. spectrum of echitamine in petrol has λ_{max} 227, 283 mμ (ε 10,000, 2360).

In support of the formulation of echitinolide as a lactone,[1] the molecular weight has been found to be 354 by the mass-spectrographic method (We are indebted to Dr. A.E. Williams, of the I.C.I. Dyestuffs Division, for this measurement); furthermore, we have shown that hydrogenolysis of

echitamine iodide ethyl ester (produced by the action of ethyl iodide on echitamine betaine, cf.[7]) also yields echitinolide.

With regard to structure (II) proposed by Robinson et al.[2] for echitamine chloride, we wish to point out that it suffers from many of the disadvantages of structure (I). In addition, the potential aldehyde group makes the failure of echitamine to be reduced by borohydride in alkaline methanol difficult to understand. Echitamine would have to have structure XI, and this would be expected to have benzenoid type of ultra-violet absorption, the p-electrons on N(a) being sterically unable to conjugate with the benzene ring.

With regard to structure (III),[3] N(a) being practically non-basic as a result of the formal positive charge on N(b), it would not be expected to form a carbinolamine system. Even if it did, being part of an eight-membered ring, one would expect it to dissociate very readily to give an α-formyl ester which should either form a carbonyl derivative or lose formic acid very easily. Similar difficulties are encountered in the formulation of echitinolide and further degradation products on the basis of (III). In a recent publication,[8] Chatterjee et al. discuss the C-nitrosation of echitamine chloride, and put forward this as further evidence for the tertiary nature of the aromatic nitrogen. In a quaternary gem-diamino system, however, the closeness of the positively charged N(b) to N(a) would afford a satisfactory explanation of the failure of a secondary N(a) to nitrosate.

We cannot yet propose a structure for echitamine which satisfactorily

---

[7] J.A. Goodson, J. Chem. Soc. 2626, (1932).

[8] A. Chatterjee and S. Ghosal, Naturwissenschaften 47, 234 (1960).

explains all the observed reactions and properties of this alkaloid. The alleged isolation of indoleacetaldehyde by periodate oxidation of echitamine chloride[3] is, for example, very difficult to reconcile with our isolation of an α,β-disubstituted indole, characterized as the crystalline methyl ester, $C_{21}H_{29}O_4N$, m.p. 142-143°, by the action of sodium in liquid ammonia on des-N-echitinolide, $C_{20}H_{23}O_4N$, m.p. 172-174°, the product of two Hofmann degradations of echitinolide. The final solution of this fascinating and complex structural problem awaits further experimental work.

1960

Tetrahedron Letters No. 20, pp. 1-2, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

DIE LIGNANE DES ÜBERWALLUNGSHARZES DER FICHTE

K. Weinges

Aus dem Organisch-chemischen Institut der Universität

und dem Forschungsinstitut für die Chemie des Holzes

und der Polysaccharide, Heidelberg

(Received 19 July 1960)

AUS dem Überwallungsharz der Fichte (Picea excelsa) isoliertes (+)-Pinoresinol (I) (Schmp. 120-121°, $[\alpha]_D^{25}$ = + 82.4°, 2% in Aceton) enthält stets (+)-Epi-pinoresinol (II) (Schmp. 137-138°, $[\alpha]_D^{25}$ = + 130.4°, 2% in Aceton); beide Lignane werden im Gegenstrom getrennt. Außerdem enthält das Harz (+)-Lariciresinol (III), (+)-Iso-lariciresinol (IV) und (-)-Seco-iso-lariciresinol (V).

Die Hydrierung von (+)-Pinoresinol, (+)-Epi-pinoresinol und (+)-Lariciresinol führt zu (-)-Seco-iso-lariciresinol; diese 4 Lignane besitzen an den deiden die Phenylpropanreste verbindenden C-Atomen die gleiche Konfiguration. Auch mit (-)-Dihydro-guajakharzsäure (Dihydroguaiiaretic acid) (VI) stimmen diese Lignane in der Konfiguration überein;[1] da für VI die absolute Konfiguration bekannt ist,[2,3] folgt für diese beiden

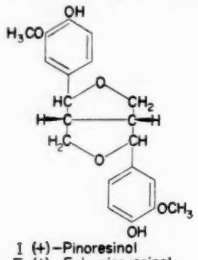
---

[1] Für die Beziehung zwischen (+)-Pinoresinol und (-)-Dihydro-guajakharzsäure haben dies bereits R.D. Haworth und D. Woodcock [J.Chem.Soc. 1054 (1939)] sowie A.W. Schrecker und L.J. Hartwell [J.Amer.Chem.Soc. 77, 432 (1955)] festgestellt.

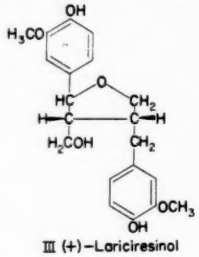
[2] A.W. Schrecker und L.J. Hartwell, J.Org.Chem. 21, 381 (1956); J.Amer. Chem.Soc. 79, 3827 (1957).

[3] B. Carnmalm, Ark.f.Kemi 15, 215 (1960).

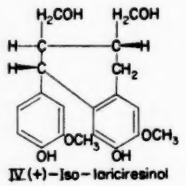
Kohlenstoffatome dasselbe bei (+)-Pinoresinol, (+)-Epi-pinoresinol, (+)-Lariciresinol und (-)-Seco-iso-lariciresinol.



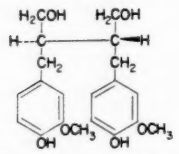
I (+)-Pinoresinol
II (+)-Epi-pinoresinol



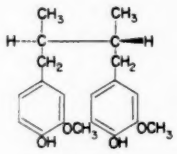
III (+)-Lariciresinol



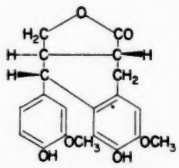
IV (+)-Iso-lariciresinol



V (-)-Seco-iso-lariciresinol



VI (-)-Dihydroguajakharzsäure



VII (-)α-Conidendrin

(+)-Pinoresinol ist symmetrisch gebaut;[4] (+)-Epi-pinoresinol unsymmetrisch.[5] Da die Konfiguration der mittelständigen CH-Gruppen übereinstimmt, wird beim Übergang von Pinoresinol zu Epi-pinoresinol eine der Äthergruppen umgelagert. (+)-Lariciresinol, das bei der vorsichtigen Reduktion des (+)-Pinoresinols entsteht, stimmt mit diesem auch in der Konfiguration der Äthergruppe überein. In den Formeln I-III ist über die absolute Konfiguration der Carbinolätherbindungen nichts ausgesagt.

(+)-Iso-lariciresinol entsteht nicht erst bei der Aufarbeitung, sodern ist ein Bestandteil des Überwallungsharzes. (+)-Iso-lariciresinol läßt sich aus (-)α-Conidendrin (VII), dessen absolute Konfiguration bekannt ist,[6] durch $LiAlH_4$ gewinnen.

---

[4] H. Erdtman, Svensk Kem.Tidskr. 48, 236 (1936).

[5] J. Gripenberg, Acta Chem.Scand. 2, 82 (1948).

[6] A.W. Schrecker unf L.J. Hartwell, J.Amer.Chem.Soc. 77, 432 (1956).

Tetrahedron Letters No. 20, pp. 3-6, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

DIE ABSOLUTE KONFIGURATION DES SESAMINS UND PINORESINOLS

K. Freudenberg und G. S. Sidhu

Aus dem Organisch-chemischen Institut der Universität

und dem Forschungsinstitut für die Chemie des Holzes

und der Polysaccharide, Heidelberg

(Received 19 July 1960)

(+)-SESAMIN (I) (Schmp. 121-122°, $[\alpha]_D^{25}$ = + 71°, 1,3 Gewicht% in Chloroform) kann in (+)-Asarinin (II) (Schmp. 121-123°, $[\alpha]_D^{25}$ = + 120°)[1,2] und in (+)-Epi-asarinin (III) (Schmp. 168-171°, $[\alpha]_D^{25}$ = + 385°)[3] umgelagert werden. Bei der Hydrierung haben wir aus diesen drei Substanzen dasselbe (-)-Dihydro-cubebin (VII) erhalten, das schon Bruchhausen und Gerhard[4] aus (+)-Sesamin gewonnen hatten; aus (-)-Asarinin erhielten sie (+)-Dihydro-cubebin. I, II und III haben demnach an den die C_6C_3-Einheiten verbindenden C-Atomen dieselbe Konfiguration. Huang-Minlon[5] sowie Kaku und Ri[6] haben (-)-Asarinin durch Entmethylenierung, Umlagerung und Methylierung in (-)-Pinoresinol-dimethyläther verwandelt; ferner hat Erdtman[7] aus (+)-Sesamin und (+)-Pinoresinol

---

1 S. Bertram, J.v.d. Steur und H. Waterman, Biochem. Z. 197, 1 (1928).

2 T. Kaku, N. Kutani und J. Takahashi, J. Pharm. Soc. Japan 56, 80 (1936); Chem. Zentr. 36, II, 2925 (1936).

3 M. Beroza, J. Amer. Chem. Soc. 78, 5082 (1956).

4 F.v. Bruchhausen und H. Gerhard. Ber. Dtsch. Chem. Ges. 72, 830 (1939).

5 Huang-Minlon, Ber. Dtsch. Chem. Soc. 70, 951 (1937).

6 T. Kaku und H. Ri, J.Pharm.Soc.Japan 57, 289 (1937); Chem. Zentr. 38, I, 3217 (1937).

7 H. Erdtman und Z. Pelchowicz, Chem. & Ind. 567 (1955).

das gleiche (+)-Bis-hydroxymethyl-bernsteinsäure-lacton (VIII) erhalten; das bedeutet, daß (+)-Sesamin (I) und seine Umlagerungsprodukte (II und III) an den genannten Kohlenstoffatomen die gleiche absolute Konfiguration wie (+)-Pinoresinol (IV) und (+)-Epi-pinoresinol (V) (voranstehende Abhandlung) haben. Sie ist in den folgenden Formeln zum Ausdruck gebracht.

Demnach unterscheiden sich die rechtsdrehenden Lignane der Sesaminreihe in der Konfiguration der Carbinol-äther-gruppe. Die positive Drehung steigt vom (+)-Sesamin (I) zum (+)-Asarinin (II) zum (+)-Epi-asarinin (III). Dies ist nur möglich, wenn die beiden Äthergruppen des (+)-Sesamins die Konfiguration der D-(-)-Mandelsäure (IX)[8] oder des (-)-Ephedrins (X)[9] oder des (+)-Catechins (XI)[10] haben. Diese 3 Substanzen erleiden bei der Umkehrung der Carbinol- oder Carbinol-äthergruppe eine kräftige Verschiebung nach rechts. Der Verschiebungssatz des optischen Drehungsvermögens ist in diesem Fall ohne Einschränkung anwendbar. Für die Gruppe des (+)-Sesamins folgen daraus die alsoluten Konfigurationen I, II und III.

Beroza,[3] der das (+)-Epi-asarinin (III) aufgefunden hat, hat zugleich beobachtet, daß es im Gleichgewicht der Umlagerung hinter (+)-Asarinin und (+)-Sesamin zurücktritt. Er folgert daraus, daß die Benzolkerne des Epi-asarinins sich räumlich behindern und teilt ihm deshalb die diaxiale Form entsprechend III zu. Das Raummodell zeigt jedoch, daß sich die Benzolkerne in III nicht behindern. Als Erklärung für die relative Labilität des Epi-asarinins dürfte die diaxiale Konformation genügen.

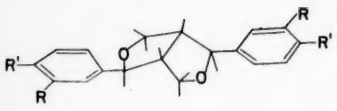
---

[8] K. Freudenberg, F. Brauns und H. Siegel, Ber. Dtsch. Chem.Ges. 56, 193 (1923); K. Freudenberg und L. Markert, Ibid. 58, 1953 (1925).

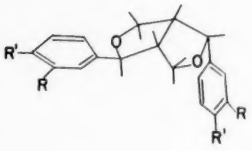
[9] K. Freudenberg und F. Nikolai, Liebigs Ann. 510, 223 (1934).

[10] K. Freudenberg; Sci. Proc. Roy. Soc. (Dublin) 27, 153 (1956).

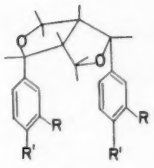
1960



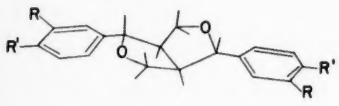
identisch mit:



identisch mit:

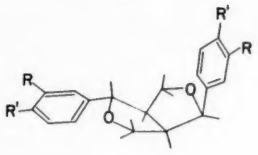


identisch mit:



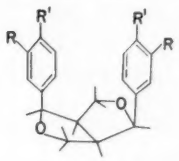
I R,R'= —O—CH_2—O— :

(+) – Sesamin



II R,R' = —O—CH_2—O— :

(+) – Asarinin



III R,R' = —O—CH_2—O— :

(+) – Epi – asarinin

IV R = OCH_3 , R' = OH:

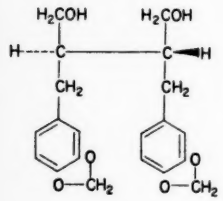
(+) – Pinoresinol

V R = OCH_3 , R' = OH :

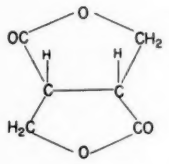
(+) – Epi – pinoresinol

VI R = OCH_3 , R' = OH :

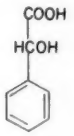
(+) – Dia – pinoresinol



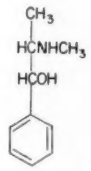
VII (–) – Dihydro – cubebin



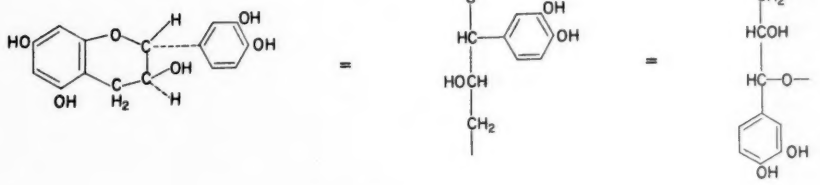
VIII (+) – Bis – hydroxy – methyl – bernstein – säure – lacton



IX D–(–)–Man – delsäure



X (–) – Ephe – drin



XI (+) – Catechin

Pinoresinol ist symmetrisch,[11] Epi-pinoresinol unsymmetrisch[12] gebaut. (+)-Epi-pinoresinol (V) dreht weiter nach rechts als (+)-Pinoresinol (IV) (vorangehende Abhandlung). Nach der Umlagerung der Dimethyläther von (+)-Pinoresinol und (+)-Epi-pinoresinol findet sich in geringer Menge ein höher drehendes Isomeres, das auch Erdtman[13] beobachtet hat. Die Reindarstellung des Dimethyläthers dieses (+)-Dia-pinoresinols (IV), wie wir es nennen, ist uns auch noch nicht gelungen. Die Zuteilung der Formeln IV, V und VI für (+)-Pinoresinol, (+)-Epi-pinoresinol und (+)-Dia-pinoresinol erfolgt aus denselben Gründen wie in der Reihe des Sesamins.

Die von Lund[14] wiedergegebene Raumformel stellt ein Derivat des (-)-Pinoresinols dar.

---

[11] H. Erdtman, Svensk Kem. Tidskr. 48, 236 (1936).

[12] J. Gripenberg, Acta Chem. Scand. 2, 82 (1948).

[13] H. Erdtman, Svensk Kem. Tidskr. 48, 236 (1936).

[14] E.W. Lund, Acta Chem. Scand. 14, 496 (1960).

Tetrahedron Letters No. 20, pp. 7-8, 1960. Pergamon Press Ltd. Printed in Great Britain

SYNTHESE VON ACETAMIDO-METHYLEN-BERNSTEINSÄURE

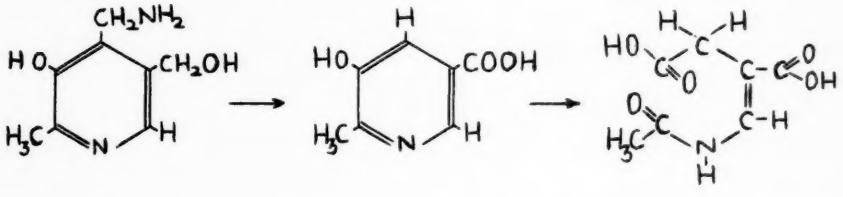
F. Lingens und R. Hankwitz

Chemisches Institut der Universität Tübingen

Biochemische Arbeitsgruppe

(Received 19 July 1960)

Beim oxydativen Abbau von Pyridoxamin (I) durch eine Pseudomonasart entsteht nach R.W.Burg, V.W.Rodwell und E.E.Snell[1] zunächst in einem fünfstufigen Abbau 2-Methyl-3-hydroxypyridin-5-carbonsäure (II). Aus dieser Pyridin-Verbindung wird durch oxydative Ringöffnung schliesslich Acetamido-methylen-bernsteinsäure (Schmp. 193-196°)(III) gebildet:



I II III

Die Synthese der Acetamido-methylen-bernsteinsäure gelang uns kürzlich auf folgendem Wege: Formylbernsteinsäurediäthylester wird durch Erhitzen mit Acetamid zu Acetamido-methylen-bernsteinsäurediäthylester (Schmp. 94°) kondensiert. Sehr milde alkalische Verseifung führt zum Acetamido-methylen-bernsteinsäure-monoäthylester (Schmp. 174°). Aus diesem Monoester lässt sich durch kurzzeitige, stark alkalische Versei-

[1] R.W.Burg, V.W.Rodwell u. E.E.Snell, J.Biol.Chem. 235, 1164 (1960).

fung und vorsichtige Neutralisation die säure- und alkalilabile Acetamido-methylen-bernsteinsäure (III) darstellen.

Schmp. 208-210° (Zers.).

$C_7H_9NO_5$ (187,2) Ber.: C 44,92, H 4,85, N 7,48

Gef.: 45,04, 4,95, 7,46.

(UV-Maximum: in n/10 HCl 265 mμ , in n/10 NaOH 261 mμ).

Der Deutschen Forschungsgemeinschaft und dem Fonds der Chemischen Industrie danken wir für eine Sachbeihilfe, den Farbenfabriken Bayer für Ueberlassung von Chemikalien.

Tetrahedron Letters No. 20, pp. 9-12, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

THE STRUCTURE OF LYCODINE

F.A.L. Anet and M.V. Rao

Department of Chemistry, University of Ottawa,

Ottawa, Canada

(Received 26 July 1960)

AYER and Iverach[1] have recently discovered the presence of an N-methyl group in the Lycopodium alkaloids α- and β-obscurine. They have suggested structures for these alkaloids on the basis of dehydrogenation experiments of Moore and Marion[2] and of a biogenetic relationship to lycopodine[3]. They have also suggested[1] a relationship of β-obscurine to lycodine, which they have recently proven[4].

We now wish to present evidence which rigorously establishes these suggested structures as correct and furthermore completely defines the relative stereochemistry of these alkaloids. This has been done by relating lycodine to lycopodine, the structure and stereochemistry of which are

---

1 W.A. Ayer and G.G. Iverach, Tetrahedron Letters No. 10, 19 (1960).

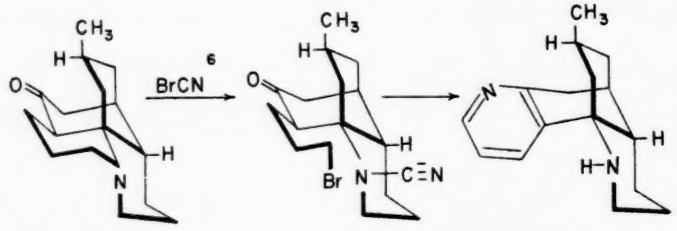
2 B.P. Moore and L. Marion, Canad. J. Chem. 31, 952 (1953).

3 W.A. Harrison and D.B. MacLean, Chem. and Ind. 261 (1950).

4 W.A. Ayer, private communication. Paper presented at the Chemical Institute of Canada Annual Conference, Ottawa, June, 1960.

known[5].

β-Cyanobromolycopodine[6] (II), available as the minor product from the reaction of lycopodine (I) with cyanogen bromide, was heated with a suspension of sodium azide in acetone. The reaction product contained intense bands at 1700 cm^{-1} (ketone), 2095 cm^{-1} (azide group), and at 2200 cm^{-1} (cyano group), and was directly reduced to a base by means of hydrogen in the presence of palladium-charcoal in acidic ethanol. This indirect method was chosen as it was known[3,6] that II underwent cyclization easily under alkaline conditions to form a very inert enol ether. The base, which partially cyclized under the isolation conditions, was dehydrogenated under mild conditions (boiling p-cymene and palladium-charcoal for 1.5 hours, conditions under which lycodine was known to be stable) and then heated with hydrochloric acid to remove the cyano group. The base, obtained in good yield, crystallized readily and was identified as lycodine by m.p., mixed m.p., ultraviolet and infrared spectra.



I II III

---

5 F.A.L. Anet, Tetrahedron Letters, No. 20, 13 (1960).

6 D.B. MacLean, R.H.F. Manske and L. Marion, Canad. J. Res. 28B, 460 (1951).

Therefore, lycodine has the relative stereochemistry shown in III and β-obscurine is the α-pyridone, and α-obscurine the 3,4-dihydropyridone analogues of III.

The structure III is completely consistent with our unpublished degradation work on lycodine. In particular, the large (0.34 p.p.m.) shift in the position (only) of the γ-proton of the pyridine ring in the NMR spectrum of lycodine on acetylation finds a ready explanation in the proximity of the γ-proton and the secondary nitrogen atom in III. This is in agreement with previous deductions[7] based on the abnormal chemical shift of the γ-proton with respect to the α- and β-protons. Unlike the results at 40 Mc., it has now been found that at 60 Mc. the methyl group of lycodine is a doublet, although poorly resolved, whilst the acetyl derivative gives a single, but broad line, for this group. The acetyl methyl group is a single very sharp line. The reasons for these effects will be discussed in a separate paper.

α-Obscurine gives[2] 7-methylquinoline and 6-methyl-α-pyridone on dehydrogenation. The cleavage into two fragments probably involves reverse Mannich-type reactions, which would not be expected to take place with lycodine. In fact, dehydrogenation of lycodine with palladium-charcoal at 250° did not give any quinoline derivatives, but a number of compounds, as shown by paper chromatography. These

---

[7] F.A.L. Anet and C.R. Eves, Canad. J. Chem. 36, 902 (1958).

compounds all appear to be substituted m-phenanthrolines as shown by their ultraviolet absorption spectra. This is not unexpected for the dehydrogenation of structure III.

We are most grateful to Dr. Léo Marion for a very generous gift of lycopodine and to the National Research Council of Canada for a grant.

Tetrahedron Letters No. 20, pp. 13-17, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

STRUCTURE, STEREOCHEMISTRY AND INTERRELATION OF SOME LYCOPODIUM ALKALOIDS

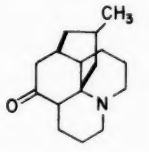
F.A.L. Anet

Department of Chemistry, University of Ottawa,

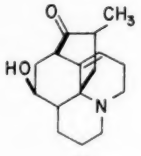
Ottawa, Canada

(Received 26 July 1960)

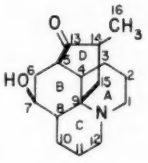
A considerable amount of degradative work has been carried out recently on lycopodine[1], acrifoline[2], and on annofoline[3], which has led to assignments of structures I, II and III respectively for these Lycopodium alkaloids.



I



II



III

However, these structures are not completely certain. We have now succeeded for the first time in interrelating these three alkaloids, a result which establishes their structures

---

1 W.A. Harrison and D.B. MacLean, Chem. and Ind. 261 (1960), and references therein.

2 W.N. French and D.B. MacLean, Chem. and Ind. 659 (1960), and references therein.

3 F.A.L. Anet and N.H. Khan, submitted for publication. F.A.L. Anet and N.H. Khan, Canad. J. Chem. 37, 1589 (1959).

rigorously. Moreover the relative stereochemistry of these alkaloids is also established by this work.

Catalytic hydrogenation of acrifoline hydrobromide (pure by paper chromatography) gave not only the known dihydroacrifoline[1], m.p. 168-172°, but also about 10% of annofoline, which was separated by preparative paper chromatography and identified by m.p., mixed m.p. and infrared spectrum. Thus the previously known dihydroacrifoline and annofoline are diastereoisomeric at C_4.

Previously[3], a compound, m.p. 88-92°, to which structure I was assigned, was obtained from annofoline, but this was not identical with lycopodine, m.p. 115°, and the compounds were thought to be diastereoisomers. It is now shown that they differ in the configuration of the carbon atom (C_{14}) bearing the methyl group.

The reduction of annofoline with $NaBH_4$ in boiling aqueous ethanol was reported[3] to give a mixture of α- and β-dihydroannofoline (the latter identical[3] to deacetylfawcettiine[4]), and these compounds are now shown not to be epimeric alcohols as might be thought. Indeed, reduction with $NaBH_4$ under neutral conditions, or with $LiAlH_4$ in ether, gave only the α-isomer. In the presence of sodium hydroxide, $NaBH_4$ gave as much as 50% of the β-isomer, which is therefore not a reduction product of annofoline, but of a ketone having the methyl group in the opposite configuration to that of annofoline. This was confirmed by the non-identity of O-acetyl-

---

[4] R.H. Burnell, J. Chem. Soc. 3091 (1959).

annofoline hydrobromide[5] and of dehydrofawcettiine[3,6] hydrobromide, even though both compounds[5,6] were hydrolyzed to annofoline by base. Thus, annofoline is the stable isomer, but under alkaline conditions it must be isomerized to some extent to the less stable ketone, which is reduced faster than annofoline.

Since annofoline and acrifoline exist[2,3,5] as mixtures of hemiketal and internally hydrogen-bonded hydroxyketone forms, ring D must exist predominantly in the boat form. Indeed, in the chair form there is a very strong repulsion between C_{14} and the axial hydroxyl group on C_7. Also, since annofoline was shown above to be the stable isomer at C_{14}, it may be deduced that the methyl group is equatorial on ring D in the boat form as in IV.

If the hydroxyl group were not present at C_7, and even more so if a double bond were present at 6,7 or 7,8, then the chair form of ring D should be the preferred conformation. In this conformation the stable isomer at C_{14} (i.e. equatorial methyl group as in V) has the opposite configuration to that in IV.

Compound V was consequently prepared by the chromium trioxide-pyridine oxidation of anhydrodeacetylfawcettiine[4]

---

5 F.A.L. Anet and N.H. Khan, unpublished.

6 R.H. Burnell and D.R. Taylor, submitted for publication. We wish to thank Dr. Burnell for informing us that dehydrofawcettiine gave annofoline on hydrolysis.

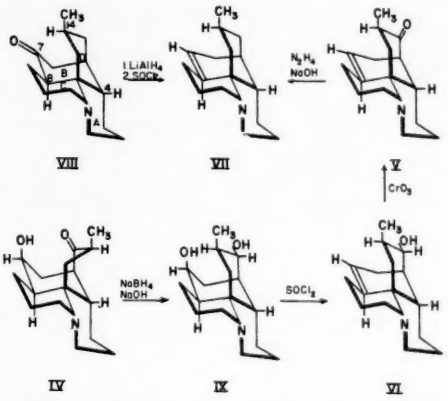
(VI), previously prepared by Burnell from deacetylfawcettiine, and hence available from annofoline by the reactions previously discussed. The oily ketone (V), $\nu_{max.}$ (CCl_4) 1705 cm^{-1}, gave a perchlorate, m.p. 190°. Calc. for $C_{16}H_{23}ON.HClO_4$: C, 55.67; H, 7.00%. Found: C, 55.08; H, 7.10%. Wolff-Kishner reduction of the ketone gave an oily base, identified as anhydrodihydrolycopodine (VII) by its infrared spectrum, and by the m.p., mixed m.p., infrared spectrum and rotation of its perchlorate. Compound VII has been obtained[7] from lycopodine by reduction with $LiAlH_4$ followed by dehydration. We have found that the dehydration step proceeds under very mild conditions, and the NMR spectrum shows that VII is the $\Delta^{7,8}$ isomer.

As anticipated, Wolff-Kishner reduction of dehydrofawcettiine gave largely the isomerized product, although traces of dihydrolycopodine may have been present.

The stability of lycopodine and dihydrodeoxyannofoline[3] to base shows that rings B and C are fused trans, a conclusion supported by the ready dehydration of dihydrolycopodine to the $\Delta^{7,8}$ isomer. Rings A and B must be fused cis to allow formation of a cyclic compound from α-cyanobromolycopodine[1] by internal alkylation at either C_6 or C_8. This is also consistent with the resulting assignment of trans-fused rings A and B in the major hydrogenation product of acrifoline, as hydrogenation would be expected to take place from the less hindered side of the double bond.

---

[7] B. Douglas, D.G. Lewis and L. Marion, Canad. J. Chem. 31, 272 (1953).



Thus lycopodine is VIII and annofoline is IV. The chair form of ring D for β-dihydroannofoline (IX) should be favoured as in the boat form the methyl group is in the unfavourable flag-pole position. Evidence for this comes from the fact[5] that neither fawcettiine nor lofoline, which are epimeric[3] at C_{17} and have the 7-hydroxyl group acetylated are hydrogen bonded in dilute CCl_4 solutions. Burnell and Taylor[6] have recently observed that VI is stable to further dehydration and have concluded that the hydroxyl group is trans to the methyl group, in agreement with the above conclusions. They have also suggested that these groups are diaxial, with ring D in the boat form, but from our results this does not appear to be the stable conformation.

The present work establishes the structures of a number of other alkaloids, previously related to compounds discussed above, and these will be enumerated in a full paper.

This work was supported by the National Research Council, Ottawa.

Tetrahedron Letters No. 20, pp. 18-22, 1960. Pergamon Press Ltd. Printed in Great Britain

ÜBER SCHEINBARE DISSOZIATIONSKONSTANTEN VON CARBONSÄUREN MIT ÄQUATORIALER UND AXIALER LAGE DER CARBOXYLGRUPPE

P. F. Sommer[1], V. P. Arya[2] und W. Simon

Organisch-chemisches Laboratorium der
Eidgenössischen Technischen Hochschule Zürich

(Received 27 July 1960)

Bei epimeren Cyclohexancarbonsäuren bestehen deutliche Unterschiede in der Acidität zwischen dem Isomeren mit axialer und demjenigen mit äquatorialer Lage der Carboxylgruppe[3 4]. Die kleinere Acidität des axialen Isomeren kann darauf zurück geführt werden, dass die Solvatation des korrespondierenden Anions gegenüber derjenigen des äquatorialen Isomeren eine Hinderung erfährt[3 5]. Diese zusätzliche Hinderung der Solvatation beruht

1 Vgl. auch P. F. Sommer, Diss. ETH, Zürich, 1960.
2 Organisch-chemisches Laboratorium der Technischen Hochschule, Stockholm.
3 R. D. Stolow, J. Amer. chem. Soc. 81, 5806 (1959); M. Tichý, J. Jonáš und J. Sicher, Coll. Czech. Chem. Commun. 24, 3434 (1959).
4 J. F. J. Dippy, S. R. C. Hughes und J. W. Laxton, J. Chem. Soc. 4102 (1954).
5 Vgl. auch D. H. R. Barton, Experientia 6, 316 (1950); G. S. Hammond und D. H. Hogle, J. Amer. chem. Soc. 77, 338 (1955).

im wesentlichen auf Wechselwirkungen mit axialen Substituenten in γ-Stellung zu der ebenfalls axialen Carboxylgruppe (1:3-Wechselwirkung). Dementsprechend dürfte mindestens für gewisse Spezialfälle eine semiquantitative Abschätzung der Grösse der Dissoziationskonstanten derartiger Verbindungen auf Grund der vorhandenen 1:3-Wechselwirkungen möglich sein. In der vorliegenden Mitteilung möchten wir lediglich einige vorläufige Ergebnisse zusammenfassen. Eine eingehendere Betrachtung wird zusammen mit theoretischen Erörterungen an anderer Stelle erscheinen[6].

Die im folgenden diskutierten Dissoziationskonstanten sind ausschliesslich scheinbare Dissoziationskonstanten bzw. negative dekadische Logarithmen dieser Grössen (pK^*_{MCS}-Werte), die nach einem früher ausführlich beschriebenen Standardverfahren[7] im Lösungsmittelsystem 80 Gew.-Proz. Methylcellosolve/20 Gew.-Proz. Wasser bestimmt wurden[8]. Auf Grund der bis heute vorliegenden Ergebnisse können die pK^*_{MCS}-Werte alicyclischer Monocarbonsäuren unter gewissen Voraussetzungen entsprechend der folgenden als Regel zu bewertenden Gleichung abgeschätzt werden:

$$pK^*_{MCS} = 7{,}44 + a \cdot 0{,}25 + b \cdot 0{,}22$$

a: Anzahl 1:3-Wechselwirkungen

b: $\begin{cases} b = 1 : \alpha\text{-Me, Ringverknüpfung in } \alpha \\ b = 0 : \alpha\text{-H} \end{cases}$

6 P.F. Sommer, V.P. Arya und W. Simon, Helv. Chim. Acta in Vorbereitung.
7 W. Simon, Helv. Chim. Acta 41, 1835 (1958); W. Simon, E. Kováts, L.H. Chopard-dit-Jean und E. Heilbronner, Helv. Chim. Acta 37, 1872 (1954).
8 W. Simon, G.H. Lyssy, A. Mörikofer und E. Heilbronner, Zusammenstellung von scheinbaren Dissoziationskonstanten im Lösungsmittelsystem Methylcellosolve/Wasser, Juris-Verlag, Zürich, 1959.

Die Grösse a entspricht der Anzahl 1:3-Wechselwirkungen, wobei sowohl 1:3-COOH:H- als auch 1:3-COOH:CH_3-Wechselwirkungen mit einzubeziehen sind. Der Faktor b ist gleich 1 wenn das α-Kohlenstoffatom der Carboxylgruppe entweder eine Methylgruppe trägt oder eine Ringverknüpfungsstelle darstellt. Beim Vorhandensein eines Wasserstoffatoms an diesem α-Kohlenstoffatom ist b = 0 zu setzen.

Als Voraussetzungen für die Anwendbarkeit der dargelegten Regel scheinen zu gelten: a) Die Carboxylgruppe ist Substituent eines in der Sessel-Konstellation vorliegenden Cyclohexan- bzw. Decalin-Gerüstes, das vermutlich insofern mit weiteren Ringen anneliert sein kann, als dadurch keine beträchtlichen Abweichungen der zu berücksichtigenden 1:3-Wechselwirkungen von den Wechselwirkungen in der idealen Sessel-Konstellation eintreten. So lässt sich die Regel interessanterweise auf Säuren mit deformierten Ringsystemen wie z.B. Abietinsäure, Podocarpsäure und Lävopimarsäure anwenden. b) Polare Gruppen sind in der untersuchten Verbindung nur dann zu vernachlässigen, wenn durch diese keine Beeinflussung des pK^*_{MCS}-Wertes der sauren Funktion eintritt, die grösser als etwa 0,05 pK^*_{MCS}-Einheiten ist.

An den 21 bis heute untersuchten Säuren konnte eine Standardabweichung (95 % Sicherheitsschwelle) der gemessenen von den mit Hilfe der angegebenen Regel berechneten Werten von 0,14 pK^*_{MCS}-Einheiten ermittelt werden. Die grösste beobachtete Abweichung beträgt 0,16 pK^*_{MCS}-Einheiten. In der unten stehenden Tabelle ist die Anwendung der Regel auf einige Säuren wiedergegeben.

Tabelle 1: Anwendungsbeispiele

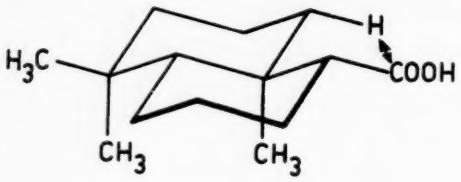
Säure	a	b	pK^*_{MCS} (gemessen)	pK^*_{MCS} (berechnet)
cis-Decalin-9-carbonsäure (I)[9]	2	1	8,17 ± 0,07	8,16
trans-Decalin-9-carbonsäure (II)[9]	4	1	8,58 ± 0,07	8,66
5,5,9-Trimethyl-trans-decalin-1-carbonsäure (III)[10]	1	0	7,80 ± 0,14[8]	7,69

Die übrigen untersuchten Verbindungen sind:

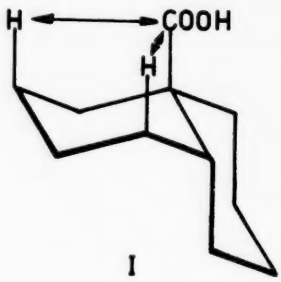
Abietinsäure, Agathendicarbonsäure-monomethylester, Cyclohexancarbonsäure, trans-4-Methyl-cyclohexancarbonsäure, cis-4-t-Butyl-cyclohexancarbonsäure, trans-4-t-Butyl-cyclohexancarbonsäure, cis-3-t-Butyl-cyclohexancarbonsäure, trans-3-t-Butyl-cyclohexancarbonsäure, Dehydroabietinsäure, Desoxypodocarpsäure, Dextropimarsäure, Dihydrodextropimarsäure, Isodextropimarsäure, Lävopimarsäure, Neoabietinsäure, Podocarpsäure, Vinhaticoesäure und Vouacapensäure.

9 R.E. Pincock, E. Grigat und P.D. Bartlett, J. Amer. chem. Soc. 81, 6332 (1959).

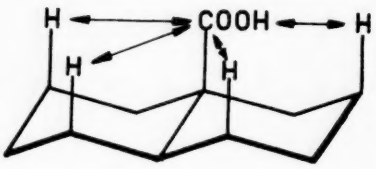
10 P.A. Stadler, A. Nechvatal, A.J. Frey und A. Eschenmoser, Helv. Chim. Acta 40, 1373 (1957).



III



I



II

Entsprechend der dargelegten Regel können experimentell ermittelte pK^{*}_{MCS}-Werte in geeigneten Fällen zur Zuordnung der relativen räumlichen Lage der Carboxylgruppe und ihrer näheren Umgebung verwendet werden.

Die Autoren sind für die Ueberlassung von Proben zur Ausdehnung der Untersuchungen sehr dankbar. Für eine Einzelbestimmung beträgt die Probemenge bei einem Molekulargewicht der untersuchten Verbindung von 250 rund 1 mg.

Tetrahedron Letters No. 20, pp. 23-24, 1960. Pergamon Press Ltd. Printed in Great Britain

DIREKT-SYNTHESE DES IRIGENINS

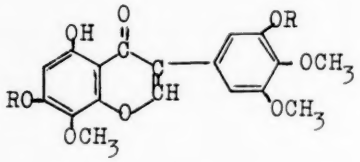
Lorand Farkas und Jozsef Varady

aus dem Institut für Organische Chemie der Technischen Universität Budapest

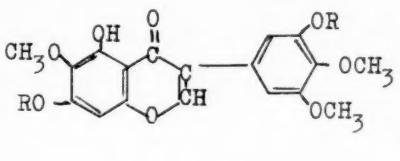
1960

(Received 1 August 1960)

Im Jahre 1893 wurde erstmals aus dem Rhizom von Iris florentina[1] Irigenin (I; R = H) isoliert.



(I)



(II)

Die Strukturaufklärung erfolgte jedoch erst im Jahre 1928[2]. Nach einer vor kurzem erschienenen vorläufigen Mitteilung gelang es Baker und Mitarbeitern[3], aus einer Mischung von Isoirigenin (I; R = H) und Irigenin (II; R = H) mit Hilfe der Papierchromatographie das Irigenin darzustellen.

---

[1] G. de Laire und F. Tiemann, Ber. 26, 2010 (1893).

[2] W. Baker, R. Robinson, J. Chem. Soc. 1022 (1928).

[3] W. Baker, D.F. Dowing, A.J. Floyd, B. Gilbert, W.D. Ollis und R.C. Russel, Tetrahedron Letters No. 5, S. 6-10, 1960.

Wir konnten das leicht darstellbare Isoirigenin[4] (I; R = H) benzylieren und in guter Ausbeute (78%) 7,3'-Dibenzyl-isorigenin (I; R = $C_6H_5CH_2$, Smp. 117°, Monoacetat Smp. 91-92°) gewinnen. Dieses Dibenzyl-Derivat wird bei der Einwirkung von Kaliumäthylat[5] in 89%-iger Ausbeute zum 5-Hydroxy-6,4',5'-trimethoxy-7,3'-dibenzyl-oxy-isoflavon (I; R = $C_6H_5CH_2$, Smp. 150-151°, Monoacetat, Smp. 172-173°) isomerisiert. Die Entbenzylierung zum Irigenin (II; R = H, Smp: 191-192°, Lit.Smp: 190.5-191.5° [3], Triacetat, Smp. 126-127°) geschieht auf katalytischem Wege.

Das synthetische Irigenin erwies sich auf Grund aller Eigenschaften mit dem natürlichen Produkt völlig identisch. Eine ausführliche Mitteilung wird in Kürze in "Chemische Berichte" veröffentlicht werden.

---

[4] L. Farkas u. J. Varady, Acta Chim. Acad.Sci.Hung. im Druck

[5] L. Farkas u. J. Varady, Chem.Ber. 93, 1269 (1960)

T.R. Seshadri u. H.L. Dhar, Tetrahedron, 7 77 (1959)

Tetrahedron Letters No. 20, pp. 25-33, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

THE STRUCTURE OF QUASSIN

Z. Valenta, A. H. Gray, S. Papadopoulos and C. Podeśva

Department of Chemistry, University of New Brunswick, Fredericton, Canada

(Received 27 July 1960)

THE constituents of *Quassia amara* have been thoroughly investigated by Robertson[1-5]. He found that the bitter extract consists of quassin, $C_{22}H_{28}O_6$, and *neo*quassin, $C_{22}H_{30}O_6$, which are in a lactone-hemiacetal relationship. Quassin contains two methoxyl groups, at least three C-methyl groups and no active hydrogen. The infrared (ν_{max} 1745, 1695, 1680, 1640 cm^{-1}) and ultraviolet spectra (λ_{max}

---

[1] E. London, A. Robertson and H. Worthington, J. Chem. Soc. 1950, 3431.

[2] R.J.S. Beer, D.B.G. Jaquiss, A. Robertson and W.E. Savige, J. Chem. Soc. 1954, 3672.

[3] K.R. Hanson, D.B. Jaquiss, J.A. Lamberton, A. Robertson and W.E. Savige, J. Chem. Soc. 1954, 4238.

[4] R.J.S. Beer, K.R. Hanson and A. Robertson, J. Chem. Soc. 1956, 3280.

[5] R.J.S. Beer, B.G. Dutton, D.B. Jaquiss, A. Robertson and W.E. Savige, J. Chem. Soc. 1956, 4850.

255 mμ, ε 11650) of quassin showed the presence of two α,β-unsaturated ketones in the molecule[3,6]. Furthermore, the results of an acidic hydrolysis of various quassin derivatives indicated that both chromophores are probably diosphenol methyl ethers[3,7].

On the basis of the fact that the selenium dehydrogenation of neoquassin yields 3,4,5-trimethylguaiacol[2], while 1,2,8-trimethylphenanthrene is obtained from the dehydrogenation of the Clemmensen reduction product of neoquassin, Beer et al. have considered the terpenoid partial structures I and II for quassin[5].

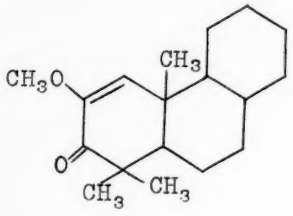
Our own investigation has established the partial structure III for quassin. The NMR spectra of quassin and neoquassin clearly show the presence of four C-methyls, with singlets at 8.15, 8.45 and 8.94, and a doublet at 8.86 (J = 7 cycles/sec). Treatment of neoquassin with $NaOCH_3$ in

---

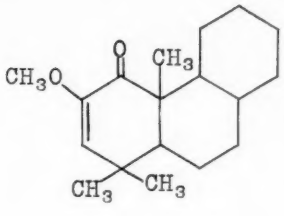
[6] Treatment of quassin with zinc and acetic acid saturates one double-bond to give dihydroquassin (λ_{max}. 252 mμ, ε 8400)(ref. 3).

[7] Acidic hydrolysis of quassin gives norquassin, $C_{21}H_{26}O_6$ (λ_{max} 258 mμ, ε 11200; λ_{max} (KOH) 258 mμ, ε 8200; 312 mμ, ε 3300), which on treatment with base undergoes a benzilic acid rearrangement to norquassinic acid, $C_{21}H_{28}O_7$ (λ_{max} 259 mμ, ε 9640). Vigorous acid treatment of norquassinic acid hydrolyses the remaining methoxyl group and yields isobisnorquassinic acid, $C_{20}H_{26}O_7$ (λ_{max} 282 mμ, ε 7910; λ_{max} (KOH) 340 mμ, ε 6000) which can be reconverted to norquassinic acid on treatment with dimethylsulphate (ref. 3).

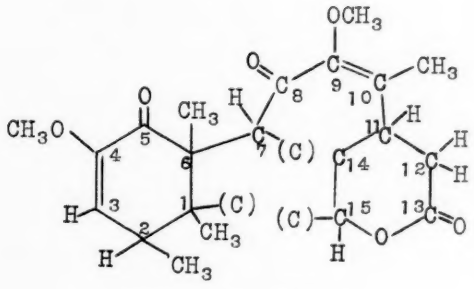
CH_3OD for 6 hours under reflux incorporates 5.5 atoms of deuterium[8]. The NMR spectrum of the deuterated neoquassin no longer contains the peak at 8.15 and the doublet at 8.86 is replaced by a triplet. Thus, one methyl group is converted to CD_3 and a $CHCH_3$ grouping to $CDCH_3$ during the treatment. The NMR spectrum of quassin shows the presence of one vinylic hydrogen (doublet at 4.77; J = 2 cycles/sec). The signal at 4.77 disappears when quassin and its derivatives are reduced to the corresponding dihydrocompounds with zinc



I



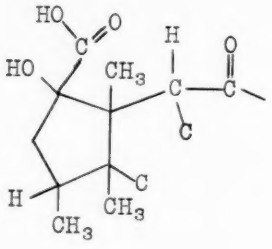
II



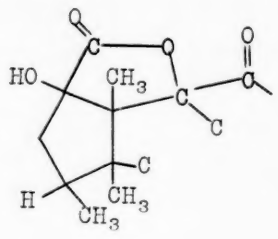
III

[8] The compound can be recovered quantitatively after a similar treatment in CH_3OH.

and acetic acid. The reflux of dihydrodesoxoquassin[9] (no vinylic H in NMR) with CH_3ONa in CH_3OD yields a deuterated product which, according to its NMR spectrum, contains the $CHCH_3$ grouping intact (doublet at 9.10)[8]. Since the vinylic hydrogen also disappears in the formation of norquassinic acid (partial formula IV), these findings clearly define the C_2-C_5 chain in quassin (see formula III).



IV



V

According to Hanson et al.[3], the treatment of norquassinic acid IV, $C_{21}H_{28}O_7$, with acetic anhydride - sodium acetate yields a neutral acetate, $C_{23}H_{28}O_7$, with a modified UV spectrum (λ_{max} 224 mμ, ε 6000; 284 mμ, ε 4200), ν_{IR} ($CHCl_3$) 1770, 1740 cm^{-1}, which can be reconverted to IV on basic hydrolysis. It is clearly an enol-lactone and its IR frequency indicates a 1,5-relationship of the carboxyl and ketone carbon atoms. Oxidation of IV with lead tetraacetate in acetic acid at room temperature gives the lactone V,

---

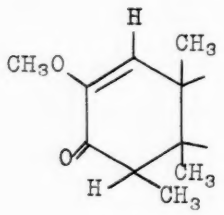
[9] In the desoxo-series, the quassin lactone ring has been replaced by a cyclic ether (ref. 4).

1960

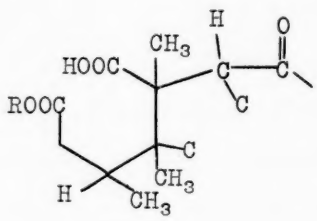
m.p. 210-214°, (Found: C, 64.64; H, 6.70; O, 29.06. $C_{21}H_{26}O_7$ requires: C, 64.59; H, 6.73; O, 28.68), (λ_{max} 269 mμ, ε 8000; ν_{IR} (KBr) 1785, 1735, 1670, 1630 cm^{-1}). Both the enol-lactone and compound V show the four C-methyl groups, including the $CHCH_3$ group, in their NMR spectra. Furthermore, the spectrum of V contains no hydrogens unshielded by the newly created lactone ring which must therefore have closed at a tertiary carbon atom. The formation of V, which is best explained by an oxidative attack at a position α to the ketone in IV, together with the deuteration results, eliminates the alternative partial formulation VI for quassin. Treatment of desoxonorquassinic acid[9] (partial formula IV) with conc. H_2SO_4 eliminates the elements of formic acid and gives an oily ketone (Found: C, 72.24; H, 8.43; O, 19.17. $C_{20}H_{28}O_4$ requires: C, 72.25; H, 8.51; O, 19.24). Its IR spectrum (1740, 1680, 1645 cm^{-1}) shows that the newly formed keto-group is in a 5-membered ring and the corresponding ring in quassin is therefore 6-membered.

Beer et al.[4] prepared the desoxodicarboxylic acid VII (R =H) by an oxidation of desoxonorquassin with alkaline hydrogen peroxide[9]. They reported that one of the carboxyl groups is very likely tertiary, since treatment of the diacid with methanol - HCl yielded a monoester, while the corresponding diester, prepared with diazomethane, gave a different monoester on prolonged basic hydrolysis. We find that the

monoester VII (R = CH_3), $C_{22}H_{32}O_7$, which is stable under the usual decarboxylating conditions, undergoes an oxidative decarboxylation on treatment with lead tetraacetate to give a doubly unsaturated ketone VIII, m.p. 102-106° (Found: C, 69.42; H, 8.48; O, 22.51. $C_{21}H_{30}O_5$ requires: C, 69.58; H, 8.36; O, 22.06); λ_{max} 267 mμ infl. (ε 6900), 295 mμ (ε 8500); ν_{IR} (KBr) 1740 (ester), 1645 (ketone), 1580 cm^{-1}. The NMR spectrum of this ketone shows no vinylic hydrogens and contains methyl singlets at 7.95, 8.16 and 8.94 and a doublet at 9.21. One methyl group must therefore be situated on the newly created double-bond. This unusual oxidation[10] completes the definition of the substitution of the C_5-C_8 chain in quassin (see formula III). It follows that quassin cannot contain a geminal dimethyl group.



VI



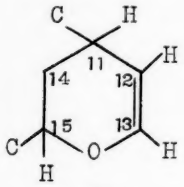
VII

[10] The reaction can be formulated as a 'vinologous 1,2-diol' oxidation of the corresponding enol-acid. We are at present investigating whether it is generally applicable for degradation of γ-ketoacids.

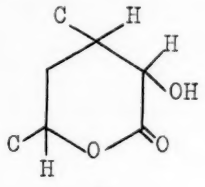
1960

The remaining features of the environment of the ketone at C_8 follow unambiguously. It is α,β-unsaturated and since C_7 has been defined by the formation of V and VIII, the double-bond must be at C_9-C_{10}. The complete deuteration of one methyl group on treatment of neoquassin with CH_3ONa in CH_3OD places the fourth methyl at C_{10}. The second methoxyl group must be at C_9, since the acid hydrolysis product of norquassinic acid (IV) shows diosphenolic properties.

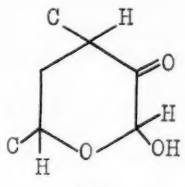
The detailed structure of the lactone ring has been established in the following way. Oxidation of anhydroneoquassin (IX)[11] with $KMnO_4$ in acetone yields three products:



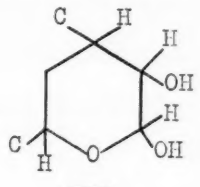
IX



X



XI



XII

(1) hydroxyquassin X, m.p. 268-270° (Found: C, 65.28; H, 6.98; O, 27.83. $C_{22}H_{28}O_7$ requires: C, 65.34; H, 6.98; O, 27.68), ν_{IR} (KBr) 1740, 1695, 1685 and 1640 cm^{-1}; (2) the ketone XI, m.p. 242-244° (Found: C, 65.03; H, 6.96; O, 27.92), ν_{IR} (KBr) 1710 infl., 1695 and 1640 cm^{-1}; (3) the

---

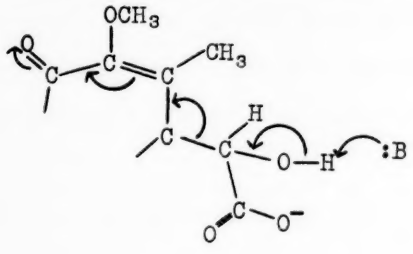
[11] Anhydroneoquassin is prepared by the treatment of neoquassin with acetic anhydride-sodium acetate. The newly created double-bond is not in conjugation with either one of the quassin chromophores (ref. 3).

alcohol XII, m.p. 235-239° (Found: C, 64.90; H, 7.48; O, 27.28. $C_{22}H_{30}O_7$ requires: C, 65.01; H, 7.44; O, 27.55). Oxidation of XII with Ag_2O in boiling ethanol converts it to X. The formation of XI shows the presence of two hydrogens at C_{12} in quassin. In agreement, the NMR spectrum of anhydroneoquassin (IX) shows, in addition to the hydrogen at C_3, two vinylic hydrogens as doublets at 3.67 and 5.48 (J = 7 cycles/sec). The presence of one hydrogen at C_{15} follows from the fact that the NMR spectra of all quassin derivatives containing the lactone ring show a triplet (1 H) at 5.75 which shifts to a higher field when the lactone carbonyl group is reduced. Oxidation of XII with periodic acid followed by basic hydrolysis and oxidation with CrO_3 in pyridine yields a γ-lactone, m.p. 266-268° (Found: C, 67.03; H, 6.86; O, 26.12. $C_{21}H_{26}O_6$ requires: C, 67.36; H, 7.00; O, 25.64), ν_{IR} (KBr) 1775, 1700, 1690 and 1635 cm^{-1}. Thus, the lactone in quassin must be 6-membered. The amorphous aldehyde-formate, obtained as an intermediate in this degradative series, shows a doublet at 0.31 (J = 6 cycles/sec.; aldehyde) and a singlet at 2.17 (formate) in its spectrum. The splitting of the aldehyde peak leaves no doubt about the presence of one hydrogen at C_{11}.

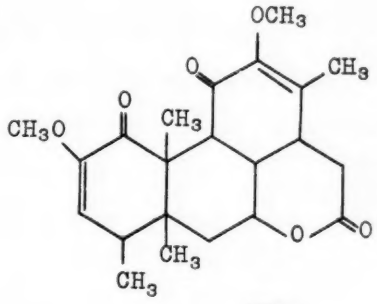
Treatment of hydroxyquassin X, $C_{22}H_{28}O_7$, with aqueous base under reflux eliminates two carbon atoms and gives a nonlactonic compound, m.p. (184)-221° (Found: C, 69.00; H,

1960

8.06; O, 22.88. $C_{20}H_{28}O_5$ requires: C, 68.94; H, 8.10; O, 22.96), ν_{IR} (KBr) 1690, 1660 and 1630 cm^{-1}. This elimination which can be visualized as shown in formula XIII establishes the relative position of the lactone ring and the ketone at C_8 in quassin[12].



XIII



XIV

On the basis of the above evidence, we propose formula XIV as the representation of quassin. It contains partial formula III and explains satisfactorily the transformation of neoquassin to the reported dehydrogenation products, 3,4,5-trimethylguaiacol[2] and 1,2,8-trimethylphenanthrene[5]. Biogenetically, its carbon skeleton can be derived from the pimarane skeleton by two 1,2-shifts.

Acknowledgements - One of us (A.H.G.) gratefully acknowledges the receipt of a National Research Council of Canada studentship. We are greatly indebted to Dr. R. S. Stuart, Merck and Co. Limited for the supply of crude quassin.

---

[12] The alternative attachment of the lactone ring at C_7 can be eliminated on the basis of evidence already presented.

Tetrahedron Letters No. 20, pp. 34-37, 1960. Pergamon Press Ltd. Printed in Great Britain

CIS-ADDITION OF FLUORINE TO A STEROID OLEFIN. A NEW ROUTE TO 6α-FLUORO-Δ^4-3-KETONES[1]

A. Bowers, E. Denot and R. Urquiza

Research Laboratories Syntex, S.A., Mexico, D.F.

(Received 14 May 1960; in revised form 1 August 1960)

It has recently been demonstrated that introduction of a 6α-fluoro substituent[2-12] to a series of steroid hormones

---

[1] Part CXLVI. R.Villotti, H.J.Ringold and C.Djerassi, J.Amer.Chem.Soc. in press.

[2] A.Bowers and H.J.Ringold, Tetrahedron 3, 14 (1958).

[3] A.Bowers and H.J.Ringold, J.Amer.Chem.Soc. 80, 4423 (1958).

[4] J.A.Hogg, G.B.Spero, J.L.Thompson, B.J.Magerlein, W.P.Schneider, D.H.Peterson, O.D.Sebek, H.C.Murray, J.C.Babcock, R.L.Pederson and J.A.Campbell, Chemistry and Industry 1002 (1958).

[5] J.S.Mills, A.Bowers, C.Casas Campillo, C.Djerassi and H.J.Ringold, J.Amer.Chem.Soc. 81, 1264 (1959).

[6] J.A.Edwards, A.Zaffaroni, H.J.Ringold and C.Djerassi, Proc.Chem.Soc. 87 (1959).

[7] A.Bowers, L.C.Ibáñez and H.J.Ringold, Tetrahedron 7, 138 (1959).

[8] A.Bowers, E.Denot, M.B.Sánchez and H.J.Ringold, ibid. 7, 153 (1959).

[9] J.A.Edwards, H.J.Ringold and C.Djerassi, J.Amer.Chem. Soc. 81, 3156 (1959).

[10] W.P.Schneider, F.H.Lincoln, G.B.Spero, H.C.Murray and J.L.Thompson, ibid. 81, 3167 (1959).

[11] S.Karaday and M.Sletzinger, Chemistry and Industry 1159 (1959).

favorably influenced biological activity. Previous approaches to these compounds had proceeded via (a) fision of a 5α-6α-epoxide with boron trifluoride etherate[2,3,5-9,11-13] or anhydrous hydrogen fluoride,[4,10] (b) trans addition of Br F to a Δ^5-3β-alcohol[14] or (c) perchloryl fluoride treatment of the derived enol ether[15] or enol acetate[16] of a Δ^4-3-ketone. All of these approaches afforded 6α-fluoro-Δ^4-3-ketones, primarily via their 6β-fluoro epimers. This communication describes the direct introduction of a 6α-fluoro substituent via the cis addition of fluorine to a Δ^5-3β-alcohol using an "in situ" preparation of lead tetrafluoride[17] as the fluorinating agent.

Δ^5-Pregnene-3β-ol-20-one acetate (I) (0.035 M) in dry methylene dichloride (200 cc.) was added to a stirred mixture of lead tetraacetate (0.07 M), anhydrous hydrogen fluoride (1.0 M) and methylene dichloride (50 cc.) at -75°. After 15 mins. at -75° the reaction mixture was neutralised with ice cold sodium carbonate solution. Chromatography of the product

---

[12] A.Bowers, L.C.Ibáñez and H.J.Ringold, J.Amer.Chem. Soc. 81, 5991 (1959).

[13] H.B.Henbest and T.I.Wrigley, J.Chem.Soc. 4765 (1957).

[14] A.Bowers, J.Amer.Chem.Soc. 81, 4107 (1959).

[15] S.Nakanishi, K.Morita and E.V.Jensen, ibid. 81, 5259 (1959).

[16] B.M.Bloom, V.V.Bogert and R.Pinson,Jr., Chemistry and Industry 1317 (1959).

[17] O.Dimroth and W.Bockemüller, Ber. 64, 516 (1931).

afforded 5α,6α-difluoropregnane-3β-ol-20-one acetate (II), m.p. 178-180°, $[\alpha]_D$ +100°.[18] Alkaline hydrolysis of II gave the corresponding 3β-alcohol (III) m.p. 221-223°, $[\alpha]_D$ +88°. Alternately, III was obtained by the direct treatment of pregnenolone with lead tetrafluoride. Oxidation of III with 8N-chromic acid[19] afforded 5α,6α-difluoropregnane-3,20-dione (IV) m.p. 224-226°, $[\alpha]_D$ +78°. Treatment of this fluoroketone with sodium acetate in methanol led smoothly to 6α-fluoroprogesterone (V), identical in every respect with an authentic sample.[2] Since 6β-fluoro-Δ^4-3-ketones are known to be stable to the conditions of this elimination reaction[14] it followed that the C-6 fluorine atom in IV and hence in II had the α-configuration. From both mechanistic and conformational considerations it followed that the C-5 fluorine atom also had the α-configuration.[20]

Molecular rotation data are in accord with the 5α,6α-stereochemistry of the difluoride, $[M]_D$ (compound II - pregnenolone) = +233.[21]

---

18 All rotations were carried out in chloroform and all new compounds analysed satisfactorily for C,H and F.

19 K.Bowden, I.M.Heilbron, E.R.H.Jones and B.C.L.Weedon, J.Chem.Soc. 39 (1946).

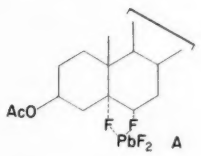
20 For a detailed discussion of the course of halogen addition to a Δ^5-double bond cf. A.Bowers, E.Denot and R.Becerra, J.Amer.Chem.Soc. in press.

21 cf. $[M]_D$ (5α,6α-dichlorocholestane-3β-ol - cholesterol) = +160, and $[M]_D$ (5β,6α-dibromocholestane-3β-ol - cholesterol) = +413. D.H.R.Barton and E.Miller, J.Amer.Chem.Soc. 72, 370 and 1066 (1950).

22 cf.ref. 21 where the stability of 5α,6β-trans dichlorides towards base treatment is discussed.

Further evidence for the cis orientation of the fluorine atoms follows from the instability of II towards alkali. Treatment of II under reflux for 1 hour with 1% methanolic potassium hydroxide solution afforded an amorphous mixture which no longer contained fluorine. A trans-difluoro compound would not be expected to lose fluorine as readily.[22]

This appears to be the first demonstration of cis addition of fluorine to an olefin[23] and presumably it proceeds via a transition state such as A.



A

Although I was stable to anhydrous hydrogen fluoride at low temperature it was observed that in the presence of a proton acceptor such as tetrahydrofuran addition of HF to the double bond took place and afforded 5α-fluoropregnane-3β-ol-20-acetate (VI)[24] m.p. 194-196°, $[\alpha]_D$ +86°. The corresponding 3β-alcohol (VII) had m.p. 188-189°, $[\alpha]_D$ +109° and upon oxidation afforded 5α-fluoropregnane-3,20-one (VIII) m.p. 204-205°, $[\alpha]_D$ +100°. Sodium acetate in methanol treatment of VIII smoothly afforded progesterone.

---

23 The original work of Dimroth and Bockemüller with PbF_4 and 1:1-diphenylethylene was later shown to involve molecular rearrangements, cf. J.Bornstein and M.Borden, Chemistry and Industry 441 (1958).

24 The configuration assigned to the fluorine atom was made by analogy with the known course of addition of hydrogen chloride to a Δ^5-steroid; cf. L.F.Fieser and M.Fieser Steroids. Reinhold Publishing Corp., New York, 1959, p. 33.

Tetrahedron Letters No.21, 1960.

NEUARTIGE DURCH BENZOPHENON PHOTOSENSIBILISIERTE ADDITIONEN VON MALEINSÄUREANHYDRID AN BENZOL UND ANDERE AROMATEN

Günther O.Schenck und Reinhard Steinmetz
Max-Planck-Institut für Kohlenforschung
Abteilung Strahlenchemie, Mülheim-Ruhr

(Received 8 August 1960)

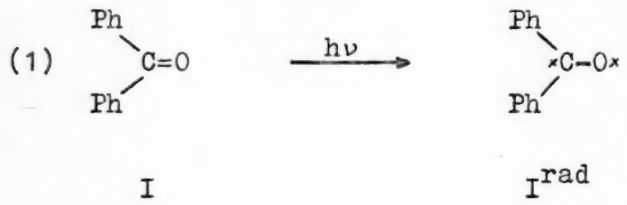
Im Jahre 1921 entdeckten W.D.Cohen und J.Böeseken[1] die durch Benzophenon (I) photosensibilisierte Autoxydation des Isopropanols (II). Sie folgt dem Bäckström'schen Prinzip[2] der primär dehydrierend photosensibilisierten Autoxydation. Nach photochemischer Initiation (1) wirkt der biradikalisch angeregte Sensibilisator I^{rad} entsprechend (2) primär auf die oxydablen Verbindungen RH wie II univalent dehydrierend ein. Anschließend reagiert O_2 mit den nach (2) entstandenen Radikalen summarisch nach (3) unter Bildung der Produkte und Regeneration des Sensibilisators. Die RH (Kohlen-

---

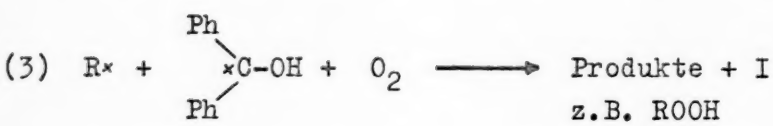
[1] J.Böeseken, Rec.trav.chim. 40, 433 (1921).

[2] H.L.J.Bäckström, The Svedberg 1884, 30.8., (festskrift) (1944); Naturwiss. 22,170 (1934). Z.physik.Chem. B 25, 99 (1934).

wasserstoffe, Aldehyde, Alkohole, Äther) gehen so durch substituierende Addition von O_2 in ROOH über, z.B. II in Isopropanol-2-hydroperoxyd[3], Tetrahydrofuran in Tetrahydrofuranhydroperoxyd[4].



I I^{rad}



Produkte + I
z.B. ROOH

Das für die durch Benzophenon photosensibilisierte Autoxydation geläufige Prinzip der primär dehydrierenden Sensibilisation zeigte sich im Austausch von O_2 gegen andere Radikalakzeptoren RA

---

[3] G.O.Schenck und H.-D.Becker, Angew.Chem. 70, 504 (1958).

[4] H.-D.Becker, Dissertation Göttingen, 1959.

1960

als vielfach variationsfähig (RA : Olefin-[5] und Acetylenderivate[6], Azodicarbonsäureester[7], Chinone, chinoide Farbstoffe, SO_2, NO, DPPH, Jod etc.[5]). Die RA werden meistens an die RH substituierend addiert zu R-RA-H.

(3') $R^{\times} + \begin{matrix} Ph \\ \times C\text{-}OH \\ Ph \end{matrix} + RA \longrightarrow$ Produkte + I
z.B. R-RA-H

Für die Bildung der Produkte ist erforderlich, daß mindestens eines der in der photochemischen Reaktionssequenz auftretenden Monoradikale, z.B. ein Semipinakonradikal, an ein RA unter Bildung eines weiteren Radikals addiert wird, was die summarische Produktbildung (3') einleitet. So erfolgt bei dem durch Benzophenon photosensibilisierten Ausbleichen von Methylenblau oder Rose Bengale in Isopropanol eine Addition eines Semipinakonradikals an das chinoide System des Farbstoffs[8].

---

5 G.O.Schenck, Angew.Chem. 69, 579 (1957).

6 aus der einzureichenden Dissertation von R.Steinmetz.

7 H.Formanek, Diplomarbeit Göttingen, 1958.

8 G.Koltzenburg, Dissertation Göttingen, 1955.

Malein- und Fumarsäure sowie ihre Ester und Halbester erwiesen sich der durch Benzophenon photosensibilisierten substituierenden Addition an Isopropanol zu Terebinsäure[9] bzw. Terebinsäurederivaten leicht zugänglich. Dies war jedoch bei Maleinsäureanhydrid (MSA) nicht der Fall.

Zur Klärung der Sonderstellung des MSA versuchten wir, dieses an o-Xylol in den Methylgruppen substituierend anzulagern. Als Strahlenquelle diente eine wassergekühlte Tauchlampe aus Glas, ausgerüstet mit einem Quecksilberhochdruckbrenner von 125 Watt. Überraschend glatt bildete sich im Verlauf weniger Stunden ein bereits bei der Belichtung auskristallisierendes Produkt $C_{16}H_{14}O_6$ (C). Dieses erwies sich als 1:2-Addukt von o-Xylol und MSA und zeigte weder chemisch noch spektroskopisch irgendwelche aromatischen Eigenschaften. Statt der erwarteten substituierenden Addition hatte zweimal eine reine Addition von MSA an die Doppelbindungen des Benzolrings stattgefunden.

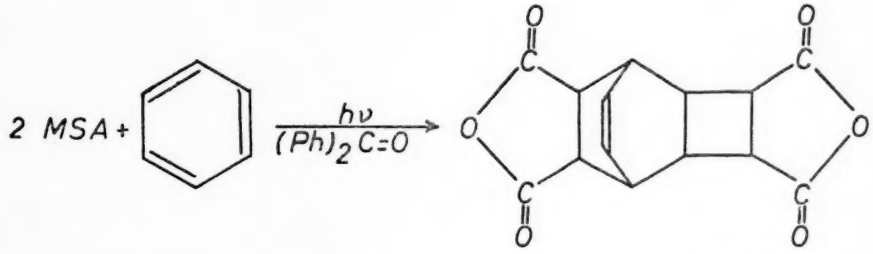
Die neuartige durch Benzophenon photosensibilisierte Addition von MSA an das aromatische System ließ sich sofort auch auf Toluol (Addukt B), Chlorbenzol (Addukt D) und Benzol (Addukt A) übertragen.

---

[9] G.O.Schenck, G.Koltzenburg und H.Großmann, Angew.Chem. 69, 177 (1957).

1960

In jedem Falle werden zwei MSA pro Benzolring addiert. Die entstehenden Dianhydride und deren Tetramethylester sind spektroskopisch nicht aromatisch. Die IR-Spektren zeigen unter sich erstaunliche Übereinstimmung, was für einen jeweils gleichen Gerüsttyp spricht.



A = III

Die Addukte A,B,C und D ließen sich auch durch direkte UV-Bestrahlung der Komponenten ohne Sensibilisator gewinnen, doch geschieht die photosensibilisierte Addition glatter und wesentlich schneller. Das aus Benzol + 2 MSA erhaltene Addukt A erwies sich als identisch mit dem nach H.J.F.Angus und D.Bryce-Smith[10] durch direkte Bestrahlung der Komponenten dargestellten Verbindung III.

---

10 H.J.F.Angus und D.Bryce-Smith, Proc.chem.Soc. 1959, 326.

Aromaten	Addukt	Fp.der 2:1 Addukte	Fp.der Tetramethyl-ester
Benzol	A	350-355° (Zers.)	135° Lit.[10]: 134°
Toluol	B	250-270° (Zers.) (infolge Isomerengemisch.)	a) 105-107° b) 163-165°
o-Xylol	C	280° (Zers.)	167°
Chlor-benzol	D	260° (Zers.)	--

Zum Mechanismus:

a) unsensibilisierte Addition

Bei UV-Bestrahlung durch Quarz oder Glas sind jeweils nur die von (gelöstem oder im Aromatenkomplex[11] vorliegendem) MSA absorbierten Quanten ($\lambda < 334$ nm) wirksam. Keine Adduktbildung bei Röntgenbestrahlung.

---

[11] L.J.Andrews und R.M.Keefer, J.Amer.Chem.Soc. 72, 3776 (1953).

1960

b) sensibilisierte Addition

Die photochemische Reaktionssequenz der nicht substituierenden Addition von MSA an Doppelbindungen enthält keine monoradikalischen Zwischenprodukte. Die Wirkung des Sensibilisators beruht hier darauf, daß der in (1) photochemisch angeregte Sens (im ersten angeregten Singulettzustand oder teilweise auch im Triplettzustand) entsprechend (2^+) mit dem gelöst oder im Komplex[11] vorliegenden MSA reagiert. Die auf (2^+) folgenden Reaktionen sind im einzelnen noch ungeklärt.

(2^+) $I^{rad} + MSA \longrightarrow MSA^{rad} + I$ oder $I^{rad}...MSA$

(2^+) erfolgt als Übertragung von Elektronenanregungsenergie oder (energetisch günstiger) unter Bildung eines kurzlebigen besonders reaktiven Additionsproduktes $I^{rad}...MSA$. I sensibilisiert auch die cis-trans-Isomerisierung von Maleinsäure in Fumarsäure[12] in einem verwandten Mechanismus.

---

[12] H.Großmann, Dissertation Göttingen, 1959.

Die photosensibilisierte Addition von MSA an Benzol wird durch Isopropanol nicht merklich gestört! Die Dehydrierung des Isopropanols in (2) wird durch MSA in dem viel wirksameren Konkurrenzprozess (2^+) selbst bei einem Molverhältnis von 10 Isopropanol zu 1 MSA noch praktisch völlig gehemmt.

Beispiel:

10 g MSA + 2 g Benzophenon in 150 ml Benzol werden wie angegeben mit dem Brenner Philips HPK 125 W unter Argonatmosphäre bestrahlt. Nach 3 Std. 1,5 g Addukt, Fp. 350-355° C; unsensibilisiert nach 3 Std. 0,3 g Addukt.

1960

HYDROBORATION OF β-PINENE

J. C. Braun and G. S. Fisher

Naval Stores Research Station[1]

Olustee, Florida

(Received 25 July 1960)

WE wish to correct our earlier[2] tentative assignment of the cis or "iso" configuration to the l-myrtanol obtained by hydroboration of β-pinene at 130° with pyridine-borane followed by oxidation of the myrtanyl borane with hydrogen peroxide and also to clarify recent reports by Dulou and Chretien-Dessiere[3] that myrtanol (methylol group trans to the gem dimethyl group) was obtained using diborane as the hydroborating agent and by Brown[4] that this reaction yielded isomyrtanol.

We have now found that myrtanol, isomyrtanol or any desired mixture of the two can be obtained by the anti-Markownikoff hydration of β-pinene by proper control of the hydroboration conditions.

---

[1] One of the laboratories of the Southern Utilization Research and Development Division, Agrilcultural Research Service, U.S. Department of Agriculture.

[2] J.C. Braun and G.S. Fisher, Abstracts of Papers, Southeastern Regional Meeting of Local ACS Sections, Gainesville, Florida Dic. 1958; FLACS, 12, No. 3, 46 (1958).

[3] R. Dulou and Y. Chretien-Bessiere, Bull.Soc.Chim.Fr. 1362 (1959).

[4] H.C. Brown, Southwestern Regional Meeting of Local ACS Sections, Baton Rouge, La., 1959.

Dupont and Zacharewicz[5] prepared l-myrtanol, (d_0^0 = 0.9858, n_D^{20} = 1.4898, $[\alpha]_D$ = 26°) by sodium reduction of myrtenol of unspecified rotation and l-isomyrtanol (d_{20}^{20} = 0.9803, n_D^{21} = 1.4925 $[\alpha]_D$ = -24.5°) by catalytic hydrogenation of l-myrtenol (from l-β-pinene). Assignment of the cis configuration to isomyrtanol was confirmed by Eigenmann and Arnold.[6] Authentic samples of l-myrtanol and l-isomyrtanol were prepared by the published methods[5,6] and purified by gas-liquid chromatography (GLC) for determination of their infrared spectra. Emergence times of the two isomers differed only slightly but there were marked differences in their spectra in the 9-11μ region. When the alcohol obtained via the reaction of pyridine-borane with β-pinene[2] was purified in the same way it was found to be identical to the authentic l-myrtanol. Hence, the tentative identification[2] as l-isomyrtanol, based on physical properties and analogy to the formation of l-isopinocampheol [m.p. 52-3°, $[\alpha]_D$ = -33° (c = 10 benzene)] from d-pinene under the same conditions,[2] was incorrect.

The following properties were found for l-myrtanol and l-isomyrtanol purified by GLC: l-myrtanol, d_4^{25} = 0.971, n_D^{25} 1.4863, $[\alpha]_D$ = -29° (C, 14.7 p-cymene), major I.R. peaks at 9.45 and 9.85 μ, l-isomyrtanol, d_4^{25} = 0.971, n_D^{25} = 1.4881, $[\alpha]_D$ = -18° (C, 17.5 p-cymene), major I.R. peaks at 9.6 (broad) and 9.95 μ.

Using Brown's general procedure[7] for hydroboration with gaseous diborane and subsequent oxidation, all at low temperature, substantially pure

---

5 G. Dupont and W. Zacharewicz, C.R. Acad. Sci., Paris 199, 365 (1934).

6 G.W. Eigenmann and R.T. Arnold, J.Amer.Chem.Soc. 81, 3440 (1959).

7 H.C. Brown and G. Zweifel, J.Amer.Chem.Soc. 81, 247 (1959).

isomyrtanol was obtained. Dulou's procedure[3] differed from that of Brown chiefly in that the temperature of hydroboration was not controlled, the solvent was removed "with as little heat as possible," and the oxidation with hydrogen peroxide was carried out in refluxing ethanol. Using this technique isomyrtanol of high purity was obtained again. However, substantially pure myrtanol was obtained when the solvent was removed after the hydroboration step by slow distillation over a period of seven hours allowing the pot temperature to rise to 140°. Samples of the myrtanyl borane withdrawn at intervals during the solvent removal and oxidized with hydrogen peroxide yielded mixtures of isomyrtanol and myrtanol.

Hence, in the case of β-pinene the hydroboration at about room temperature occurs stereospcifically from the less hindered side of the molecule, i.e. trans to the bulky gem dimethyl group, to yield the thermodynamically unstable isomyrtanyl borane as predicted.[2,7] However, subsequent heating of the borane converts it almost quantitatively to the more stable myrtanyl borane.

Positional isomerization of the alkyl boranes at about 140° is well known, but this is apparently the first case of stereoisomerization without migration of the borane group. Work is under way to explore the scope and mechanism of this isomerization to the thermodynamically stable borane.

THE POSITION OF PROTONATION AND BASICITIES OF INDOLES

R. L. Hinman and J. Lang

Union Carbide Research Institute, White Plains, New York

(Received 25 July 1960)

The weakly basic character of the indole nucleus has been a subject of continuing interest with regard to both the base strengths of the nuclei and the positions of protonation. Protonation of positions 1[1a] and 3[1b,c] have received the most support, but it has also been shown[2] that substitution of the 2-position by electrophilic species may take place when the 3-position is occupied, as in skatole.

We have obtained direct spectroscopic evidence that indole and a number of its methyl derivatives are protonated predominantly at the 3-position in strongly acidic media. In the 60 mc. n.m.r. spectrum[3] of 2,3-dimethylindole the 3-methyl resonance is split and shifted to higher fields (507 cps. relative to solvent as internal standard) than that of the 2-methyl (431 cps.). A quartet at 349 cps. is assigned to the 3-hydrogen of formula I. The coupling constant of the doublet and the quartet is ~ 7.6 cps., in accord with the

---

[1a] E.g. R. de Fazi, G. Berti and A. daSettimo, Gazz. chim. ital. 89, 2238 (1959).

[1b] A. Treibs, E. Herrmann, E. Meissner and A. Kuhn, Ann. 602, 153 (1957).

[1c] H. F. Hodson and G. F. Smith, J. Chem. Soc. 1957, 3544.

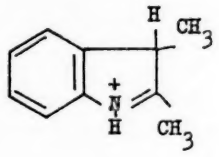
[2] W. E. Noland and D. N. Robinson, Tetrahedron 3, 68 (1958).

[3] The authors are indebted to Dr. Earl Whipple of the Union Carbide Research Institute for obtaining and interpreting the N.M.R. spectra.

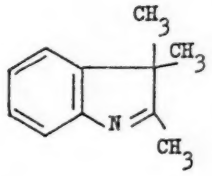
structural feature > $CHCH_3$. The spectra of skatole and 1,2,3-trimethylindole in acid show similar splitting of the 3-methyl resonance, whereas the spectrum of 1,2-dimethylindole shows three lines at 338 (CH_2), 364 (1-methyl), and 429 cps. (2-methyl) with relative areas of 2:3:3. In 6 M sulfuric acid, where the proton exchange rate is greater, the 3-methyl resonance in 1,2,3-trimethylindole was not shifted from its position in 12 M acid, but was no longer split, showing that it is the proton from the strong acid which causes the spliting.

1960

Further evidence for 3-protonation was obtained from the ultraviolet spectra of indole and its 1-, 2-, and 3-mono-, di-, and trimethyl derivatives in strong acid. These spectra resemble closely those of 2,3,3-trimethylindolenine (II) in 0.1 N hydrochloric acid (λ_{max} 229, 235, 275 mμ, log ϵ 4.00, 3.95, 3.91) and of the methiodide of II in water (λ_{max} 229, 236, 273 mμ, log ϵ 3.78, 3.73, 3.77). In 3 M sulfuric acid, for example, the spectrum of 1,2,3-trimethylindole shows λ_{max} 230, 237, 275 mμ (log ϵ 4.07, 3.99, 3.98).



I



II

While protonation occurs predominantly at the 3-position[4] in aqueous

---

[4] It has been shown by deuterium exchange studies (M. Koizumi and coworkers, Bull. Chem. soc. Japan 13, 307, 643 (1938); 14, 453 (1939)) that 3-protonation of indole occurs in mild acid and both 2- and 3-protonation take place when pH < 0.5. A very low concentration of 2-protonated indole would explain the results of the exchange experiments, which lasted at least five hours, and would be compatible with our results. The exchange work naturally did not show that protonation of the 3-position occurs even when an alkyl group is present.

acid, in solid salts of methylindoles protonation of the 1- or 3-position may take place. Thus the infrared spectrum of the salt of 2-methylindole and sulfuric acid in Nujol had a band of medium strength at 1644 cm^{-1}, indicating the presence of $>C=\overset{+}{N}H$. Bands at 2490 and 1995 cm^{-1} showed the presence of immonium and ammonium bands, respectively.[5] However, the acid sulfates of 1,2-dimethylindole and 1,2,3-trimethylindole showed bands of medium intensity near 2500 cm^{-1}, indicating formation of the ammonium group by protonation of the indole nitrogen.

The shifts in the ultraviolet spectra on protonation were also used to estimate the relative basicities of indole and some of its methyl derivatives. The spectrum of 2-methylindole is shifted completely to the protonated form in 4 M sulfuric acid. 1-Methylindole requires 6 M acid, while the spectrum of skatole shows similar changes in 9 M acid, the methyl group in the 3-position actually exerting a striking base-weakening effect, as shown in the following series of basicities: 1,2 > 1,2,3; 2 >2, 3 >1 >1,3 > indole > 3. Preliminary pKa' measurements show that 2-methylindole is several thousand times more basic than skatole. The reason for this difference is under study. 2-Methylindole-3-acetic acid is much more basic than indole-3-acetic acid, and in general the biologically significant indoles derived from skataole fall in the least basic group. This pronounced difference in basicities is also shown by the fact that all 2-alkylindoles studied (2-methyl-, 1,2-dimethyl-, 1,2,3-trimethyl-, 2,3-dimethyl- and tetrahydrocarbazole) were successfully titrated potentiometrically in nitromethane with 0.1 N perchloric acid in acetic acid as titrant. Indoles which lack the alkyl group in the 2-position could not be titrated. Analysis

---

5 B. Witkop, J. B. Patrick, and H. M. Kissman, Ber. 85, 949 (1953).

for 2-methylindole in the presence of 3-methylindole was effected by this method. Previous unsuccessful attempts[6] to titrate the indole nucleus were limited to indole itself, which is not basic enough to give a satisfactory end-point.

Quantitative measurements of the pKa's of indoles using the Hammett H_0 function are in progress.

---

[6] J. S. Fritz and G. S. Hammond, Quantitative Organic Analysis, John Wiley, New York, 1957, p. 34.

REDUCTION DU CAMPHRE PAR LES METAUX DISSOUS. OBTENTION SELECTIVE D'ISOBORNEOL

G. Ourisson et A. Rassat

Institut de Chimie, Strasbourg et Ecole Normale Supérieure, Paris

(Received 2 August 1960)

IL est très généralement admis que la réduction des cétones par les métaux dissous conduit à un mélange d'alcools dans lequel prédomine l'épimère thermodynamiquement le plus stable.[1]

La même généralisation avait été faite pour la position β des dérivés carbonylés α,β-éthyléniques. On connait maintenant divers exemples de telles réductions qui donnent de façon prépondérante l'épimère le moins stable,[2] ou bien où la nature du métal utilisé influe sur les proportions d'épimères obtenues.[3]

Dans le cas des carbonyles isolés il ne semble pas que l'on ait jusqu'ici prêté l'attention qu'il mérite au fait suivant: de nombreux

---

[1] Cf.p.ex.: D.H.R. Barton, Experientia 6, 316 (1950); J. Chem. Soc. 1027 (1953); D.H.R. Barton et R.C. Cookson, Quart. Rev. 10, 44 (1956); W. Klyne, Prog. Stereochem. I, 36 (1954); W.G. Dauben et K.S. Pitzer, dans Steric Effects in Organic Chemistry (Edited by M.L. Newman), p. 47. John Wiley, New York (1956).

[2] G. Stork et S.D. Darling, J. Amer. Chem. Soc. 82, 1512 (1960).

[3] G.E. Arth, G.I. Poos, R.M. Lukes, F.M. Robinson, W.F. Johns, M. Feurer et L.H. Sarett, J. Amer. Chem. Soc. 76, 1715 (1954).

exemples de réductions de bicyclo-2,2,1-heptanones-2 par le sodium et un alcool ont donné surtout l'épimère endo, qu'il soit le plus stable (pont disubstitué en C-7), ou le moins stable thermodynamiquement (pont méthylénique). Le Tableau 1 rassemble ces résultats.

1960

TABLEAU 1

Réduction de cétones par le sodium et un alcool

Cétone:	Pourcentage d'alcool endo
nor-camphre	77% [a,b]
méthyl-1 nor-camphre	84% [a,c]
α-fenchocamphorone	prépondérant [d,e]
β-fenchocamphorone	prépondérant [f,e]
camphénylone	86 [a]
camphre	79 [a]
fenchone	91 [a,g]
isofenchone	67 [a,h]
épicamphre	prépondérant [i]

Sont soulignés les cas où l'acool endo est le moins table.
[a] P. Hirsjärvi, Ann. Acad. Sci. Fenn. A II, 81 (1957); [b] G. Komppa et S. Beckmann, Liebigs Ann. 512, 172 (1934) [c] S. Beckmann et R. Schaber, Ibid. 585, 154 (1954); [d] O. Wallach, Ibid. 300, 294, 316 (1898); [e] S. Beckmann et R. Bamberger, Ibid. 574, 65 (1951); [f] G. Komppa et S. Beckmann, Ibid. 537, 140 (1939); [g] W. von E. Doering et T.C. Aschner, J. Amer. Chem. Soc. 71, 838 (1949); [h] H. Schmidt et K. Todenhofer, Ber. Schimmel, 111 (1937); Chem. Abstr. 32, 6234 (1938); [i] M. Lipp et E. Bund, Ber. 68, 249 (1935).

Nous résumons ici une partie des résultats d'une étude motivée par ces contradictions, et relative à la réduction du camphre par les métaux en solution. Les nombreux facteurs opératoires ont été étudiés séparément. L'analyse des mélanges obtenus a été faite par chromatographie en phase

gazeuse, et vérifiée par polarimétrie; dans tous les cas qui suivent, la réduction est totale, et le pourcentage d'isobornéol indiqué correspond à la fois à sa proportion dans le mélange et à son rendement d'obtention à partir du camphre. Deux exemples serviront à illustrer comment la variation du métal ou la variation du donneur de protons utilisés, peuvent rendre la réduction stéréosélective soit en faveur de l'alcool le plus stable, soit en faveur de l'alcool le moins stable.

Par addition de camphre dissous dans l'éther anhydre, à une solution de métal dans l'ammoniac liquid, suivie après 15 minutes d'une addition d'éthanol en axcès, on obtient les pourcentages suivants d'isobornéol, l'épimère instable, exprimés par rapport au mélange d'alcools. (Tableau 2).

TABLEAU 2

Métal:	Li	Na	K	Rb	Cs	Ca	Ba
à -33°	20	40	70	77	85	28	35
à -78°	16		46				

Par addition de métal à une solution de camphre dans l'ammoniac liquide, en présence de donneur de protons, on obtient à -33° les pourcentage suivants d'isobornéol. (Tableau 3)

TABLEAU 3

Donneur de protons:	Métal Li	K
NH_4Cl	8	10
EtOH très grand excès	16	15
EtOH léger excès		42
t-BuOH		55

Dans les Tableaux 2 et 3, nous avons souligné les valeurs qui correspondent à un excès (dans quelques cas considérable) de l'épimère instable.

Nous poursuivons l'étude de ces réductions, en série bicyclo-2,2,1-heptanique et dans d'autres séries, en vue de déterminer la généralité des observations rapportées ici, et d'en préciser les conséquences, complexes, sur le mécanisme de réduction par les métaux dissous.

Nous remercions les Professeurs S. Beckman et N.J. Toivonen pour des discussions et un échange de correspondance.

NEW TYPES OF HYDRIDE TRANSFER*

Z. N. Parnes, M. E. Volpin and D. N. Kursanov

Institute of Organo-Element Compounds,

U.S.S.R. Academy of Sciences, Moscow

(Received 13 July 1960; in revised form 19 August 1960)

THE interpretation of organic reaction mechanisms often involves hydride[1-3] transfer, but this hydride transfer has seldom been proved experimentally.[4] As the hydride ion is usually transferred to a carbonium ion, the presence of which is not easily established, it is difficult to prove experimentally that hydride transfer has actually taken place. Stable carbonium ions may be formed from cycloheptatriene or triphenylmethyl carbonium salts.[5] The conversion of tropylium ion to cycloheptatriene by the addition of a hydride ion would, therefore, be an unequivocal hydride transfer reaction.

We have established that tropylium ion readily removes a hydride ion from lithium aluminium hydride, sodium borohydride or di-isobutyl-aluminium hydride with the formation of cycloheptatriene.

---

* Translated by A.L. Pumpiansky, Moscow.

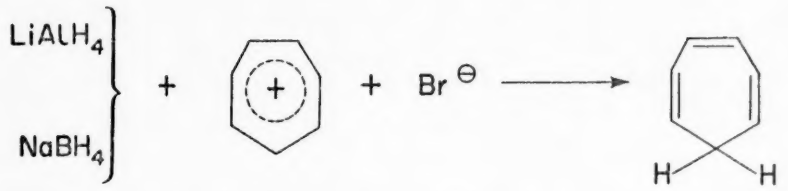
1 E.K. Alexander, Principles of Ionic Organic Reactions pp. 167-170. N.Y.L. (1950).

2 K.D. Nenitsesku, Uspekhi Khim. 26, 399 (1957).

3 N.C. Deno, H.J. Peterson and G.S. Saines, Chem. Rev. 60, 7 (1960).

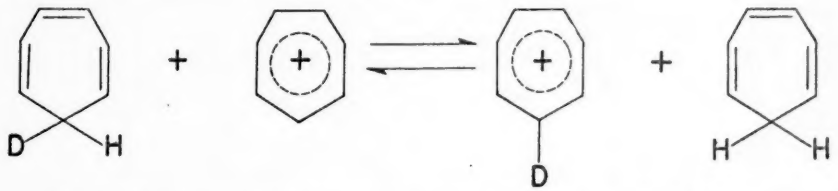
4a P.D. Bartlett, F.E. Condon and A. Schneider, J. Amer. Chem. Soc. 66, 1531 (1944); b P.D. Bartlett and J.D. McCollum, Ibid. 78, 1441 (1956).

5 J. Dauben, F.A. Gadecki, K.M. Harmon and D.J. Pearson, J. Amer. Chem. Soc. 79, 4557 (1957).



Similarly, the reaction between a tropylium salt and triethyl tin $(C_2H_5)_3SnH$ of triethyl silane $(C_2H_5)_3SiH$ results in the formation of cycloheptatriene Alcohols may also be used as hydride donors. The action of benzyl alcohol on tropylium bromide results in the formation of cycloheptatriene and benzaldehyde. We have found this reaction to have the kinetic isotopic effect. The low value of the kinetic isotopic effect shows that the rate determining step of this reaction is the hydride transfer.

Of special interest is the hydride transfer reaction using cycloheptatriene as donor. This compound readily releases a hydride ion by the action of electrophilic reagents such as PCl_5, $AlCl_3$, conc H_2SO_4 and $(C_6H_5)_3C^+$ with the formation of tropylium ion.[5,6] Further, a reversible hydride transfer may take place between cycloheptatriene and tropylium.[7]



The hydride exchange reaction between monodeuteriocycloheptatriene and tropylium ion was studied in acetic acid, methanol, ethanol and nitromethane solutions, equilibrium being reached at 20° in less than 6 hours. In Table 1 the kinetic data of this reaction in glacial acetic acid are listed. The

---

[6] D.N. Kursanov and M.E. Volpin, Dokl. Akad. Nauk SSSR 113, 339 (1957).

[7] Z.N. Parnes, M.E. Volpin and D.N. Kursanov, Izv. Akad. Nauk SSSR, Otdel. khim. nauk (1960).

reaction was run at 10,15,20 and 30°, the hydrogen exchange rate being 0.010, 0.015, 0.023 and 0.044 respectively. The activation energy proved to be 14.3 kc.

TABLE 1

Hydride Exchange Rate between Cycloheptatriene-d* and Tropylium Bromide in Glacial Acetic Acid**

Temp. (°C)	Time (min)	Deuterium*** in tropylium salts (at.%)	Reaction rate (g mole/l.min)
30	10	0.95	0.046
	15	1.23	0.043
	20	1.95	0.056
20	10	0.58	0.026
	20	0.99	0.027
	30	1.22	0.020
	40	1.46	0.019
	50	1.89	0.022
15	15	0.50	0.015
	30	0.98	0.016
	45	1.31	0.015
10	20	0.54	0.012
	40	0.92	0.012
	60	1.51	0.010
	80	1.46	0.010
	100	1.72	0.010

* Deuterium concentration: 7.7 at. %.
** Concentration of each component: 0.44 g mole/l.
*** Equilib ium deuterium concentration: 3.9 at. %.

Hydrogen exchange reaction rates were calculated in terms of the formula $Rt = - \frac{(A)\ (B)}{(A) + (B)} \ln (1-F)$[8]

This hydrogen exchange cannot result from proton hydrogen exchange as the tropylium ion does not undergo hydrogen exchange even with very strong

[8] A.C. Wahl (Editor), Radioactivity Applied to Chemistry. N.Y.L. (1951).

proton donors such as D_2SO_4 and DBr + $AlBr_3$.[9] Further, it cannot be suggested that the reaction gives rise to kinetically independent hydride ions as it takes place in media involving labile protons including acids without molecular hydrogen being evolved. The reaction may proceed via an activated complex in which the hydrogen ion is removed from the cycloheptatriene molecule and transferred to the tropylium ion. The hydrogen exchange reactions previously investigated involved a reversible transfer of proton. The exchange reaction between cycloheptatriene-d and tropylium is, therefore, the first instance of a reversible hydride transfer.

It has recently been shown[10] that the tropylium ion is capable of removing a hydride ion from ditropyl ether with the formation of tropone and cycloheptatriene.* Thus by making use of the stable tropylium ion as a hydride acceptor, we have succeded in establishing hydride transfer in a number of reactions as well as the reversible hydride transfer.

---

* To prepare tropone from ditropyl ether it is advantageous to use benzaldehyde as acceptor of hydride ions, one molecule of ditropyl ether giving two tropone molecules.

9 M.E. Volpin, K.J. Zdanova, D.N. Kursanov, V.N. Setkina and A.J. Shatenshtein, Izv. Akad. Nauk SSSR, Otdel. khim. nauk 754 (1959).

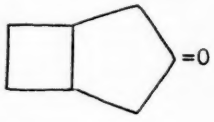
10 A.P. Ter Borg, R. van Helden, A.F. Bickel, W. Renold and A.S. Dreiding, Helv. Chim. Acta 43, 457 (1960); M.E. Volpin, Z.N. Parnes and D.M. Kursanov, Izv. Akad. Nauk SSSR, Otdel. khim. nauk (1960).

A PHOTOCHEMICAL SYNTHESIS OF BICYCLO [2.2.0]-HEXANE[1]

Sheldon Cremer and R. Srinivasan
Department of Chemistry, University
of Rochester, Rochester, N. Y.

(Received 16 August 1960)

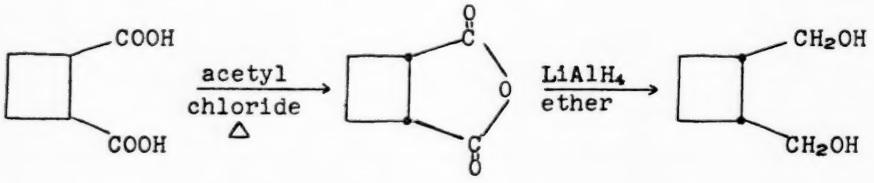
One of three methods by which a cyclobutane ring may be synthesized photochemically is the vapor phase photolysis of a substituted cyclopentanone. Photolysis of cyclopentanone itself gives rise to cyclobutane and carbon monoxide among other products.[2] One may expect that the photolysis of bicyclo [3.2.0]-heptanone-3 (I) would lead to bicyclo [2.2.0]-



I

hexane by an analogous process.

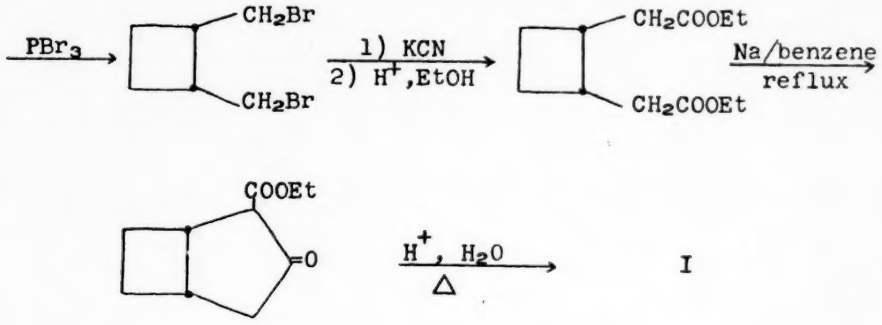
I was synthesized from cyclobutane-1,2-dicarboxylic acid by the following steps:



---

1. The authors wish to thank the National Science Foundation for a grant to the Department of Chemistry, University of Rochester, in support of this work.

2. S. W. Benson and G. B. Kistiakowsky, J. Am. Chem. Soc. 64, 80 (1942).



1960

The first four steps have been described before.[3] The fifth and sixth steps were adapted from similar processes in the literature.[3,4]

I (b.p. 107.5° at 113 mm; Found: C, 76.36; H, 9.15. Calc. for $C_7H_{10}O$: C, 76.32; H, 9.15%) had an infrared spectrum which strongly resembled that of cyclopentanone. The nuclear magnetic resonance spectrum was consistent with the bicyclic formulation. I gave rise to a semicarbazone derivative (m.p. 197-200° dec. Found: N, 25.20. Calc. for $C_8H_{13}ON_3$: N, 25.13%). The intermediate carbethoxy derivative of I (b.p. 66-67° at 0.4 mm. n_D^{25} = 1.4855. Found: C, 65.70; H, 7.63. Calc. for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74%).

Photolyses of I were carried out in a 2 liter Pyrex bulb heated to 80°. The ketone (15 mm) and carbon dioxide (150 mm) were admitted through a conventional vacuum line. Two Hanovia medium pressure mercury arcs were used as light

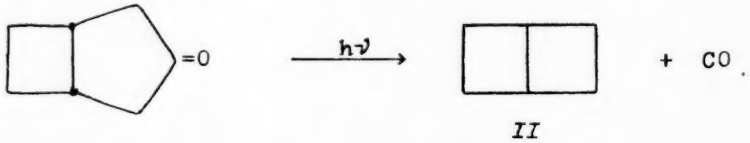
---

3. N. L. Allinger, M. Nakazaki, and V. Zalkow, ibid. 81, 4074 (1959).

4. R. P. Linstead and E. M. Meade, J. Chem. Soc. 935 (1934).

sources.

In addition to carbon monoxide and 1,5-hexadiene, which were the major products, a third product (II) was formed to a small extent. It was separated by gas chromatography and characterized by physical methods. The molecular weight as determined by mass spectrometry was 82 (C_6H_{10}). The vapor pressure at 26.5° was 100 mm. By a micro method,[5] the b.p. at atmospheric pressure was estimated to be about 90°. The infrared spectrum (solvent: CCl_4) showed strong absorption at 3.46 and 3.52 (shoulder) μ and weak ones at 6.98 and 11.0 μ. There was no evidence of unsaturation. The nuclear magnetic resonance spectrum (solvent: CCl_4; chloroform as internal standard) confirmed the absence of unsaturation and indicated that the resonances of all the protons occurred within a broad (1.26τ wide) band centered at 7.66 τ . A solution of the product in CCl_4 was sealed in a glass bulb and heated to 230° for 20 mins. The infrared spectrum of the solution then indicated the presence of vinyl group(s) and no other strong absorption. Gas chromatography showed that a product with the same retention time as 1,5-hexadiene had been formed. These facts may be interpreted to mean that II is bicyclo [2.2.0]-hexane which is formed as follows:

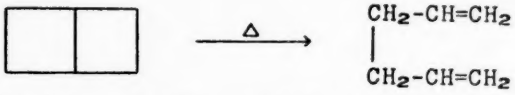


II

---

5. S. W. Benson, Ind. Eng. Chem. Anal. Ed. 14, 189 (1942).

On heating, a reaction



analogous to the thermal decomposition of cyclobutane to ethylene may have taken place. The alternative formulation of II as bicyclo [2.1.1]-hexane is not excluded by the evidence given here. But it is known from the photolysis of cyclopentanone-1,1,2,2-d_4 that a skeletal rearrangement does not accompany the photodecomposition to give cyclobutane-d_4.[6] Hence II is most probably bicyclo[2.2.0]-hexane.

It was further observed that the photochemical formation of 1,5-hexadiene and II from I was sensitive to changes in wavelength and total pressure. An increase in the wavelength or pressure favored the formation of II.

This effect is entirely similar to the influence of wavelength and pressure on the formation of cyclobutane and ethylene from cyclopentanone.[7,8] However, even under the most favorable conditions II was produced from the decomposition of I in only 5% yield. Hence this method cannot be recommended for the preparation of II in quantity.

Acknowledgement: The authors wish to thank Professors W. Albert Noyes, Jr. and D. S. Tarbell for their advice and encouragement.

---

6. R. Srinivasan, J. Am. Chem. Soc. 81, 1546 (1959).
7. F. E. Blacet and A. Miller, ibid. 79, 4327 (1957).
8. R. Srinivasan, Unpublished Results.

Tetrahedron Letters No. 22, pp. 1-4, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

THE BIOGENESIS OF HYOSCINE IN DATURA STRAMONIUM L.

A. Romeike and G. Fodor

Deutsche Akademie der Wissenschaften zu Berlin

Institut für Kulturpflanzenforschung, Gatersleben

and

Stereochemical Laboratory, The Academy, Budapest

(Received 2 September 1960)

AS previously reported[1,2,3] the stems and leaves of Datura ferox L. convert hyoscyamine into hyoscine. An intermediate product in this reaction is an alkaloid V[4], probably identical with 6-hydroxy-hyoscyamine.

It was assumed that the hyoscine in other plants e.g. Datura stramonium L., is derived similarly, but it has been established that the stems and leaves of adult plants of Datura stramonium L., Datura innoxia MILL., Datura metel L. and Atropa bella-donna L. are not able to convert hyoscyamine into hyoscine although this may be possible in the young plants. Marion and Thomas[5] and Leete[6] ascertained that 4-5 month old plants of D.stramonium L. cannot synthesize

---

1 A. Romeike, Flora 143, 67 (1956).

2 A. Romeike, Flora 148, 306 (1959).

3 G. Fodor, A. Romeike, G. Janzsó and I. Koczor, Tetrahedron Letters No. 7, 19 (1959).

4 A. Romeike, Naturwissenschaften 47, 64 (1960).

5 K. Marion and A.F. Thomas, Canad. J. Chem. 33, 1853 (1955).

6 E. Leete, J. Amer. Chem. Soc. 82, 612 (1960)

hyoscine.

Although Methyl ^{14}C atropine has been prepared by Werner et al.,[7] owing to the stereospecificity of the enzyme system in Datura to oxidize S - hyoscyamine only,[4] feeding experiments with S - methyl ^{14}C - hyoscyamine were preferred. The methyl ^{14}C - hyoscyamine was synthesized from nortropine by methylating with ^{14}C-methyl iodide, acylation of the methyl ^{14}C - tropine with S - acetyltropoyl chloride and mild deacetylation.

The feeding experiments with the labelled hyoscyamine were conducted as follows: 26, fourteen day old seedlings of Datura stramonium L.var. stramonium were cultivated for a week in an inorganic nutrient medium containing 500 µg of radioactive hyoscyamine. This solution had a hyoscyamine concentration of 0.004% and the activity, measured in a flow-counter (Frieske and Hoepfner), was 277.500 per minute. After two days all the hyoscyamine had been taken up by the seedlings and during the following five days they were cultivated in a pure nutrient medium.[2] The results of 26 control seedlings grown under corresponding conditions in the inorganic medium are given in Table 1. The percentage of radioactivity found in the hyoscine and the alkaloid was 27.5 and 9.8 respectively. These analyses were done by paper chromatography and the quantitative estimations according to de Bruyn and van Hall.[8]

In order to examine the role of the shoots in the conversion of hyoscyamine into hyoscine similar experiments were performed with the aerial shoots of Datura stramonium seedlings. The results are recorded in Table 1.

---

[7] G. Werner and E. Kassner, Naturwissenschaften 46, 649 (1959).

[8] J.W. de Bruyn and J.G. van Hall, Mededeling 152 Inst. voor de Veredel. v.Tuinbowgew.,Wageningen (1959).

1960

TABLE 1

Feeding Experiments in Datura stramonium L. var. Stramonium with ^{14}C labelled Hyoscyamine ($N\text{-}CH_3$)

	hyoscyamine fed to the plants		alkaloids found after a week						not identified radioactive substances activity (counts/min)
			hyoscine		hyoscyamine		alkaloid V		
	activity (counts/min)	quantity	activity (counts/min)	quantity	activity (counts/min)	quantity	activity (counts/min)	quantity	
26 intact seedlings, 14 days old (experimental plants) fresh weight 6,25 g, dry weight o,29 g	277 5oo	5oo γ	76 3oo	29o γ	62 57o	13o γ	27 1oo	6o γ	14 5oo
26 intact seedlings, 14 days old (control plants) fresh weight 6,1o g, dry weight o,3o g	-	-	-	14o γ	-	2o γ	-	traces	-
alkaloids built by conversion of hyoscyamine			76 3oo	15c γ			27 1oo	6oγ	14 5oo
			(27,5 % of the total activity fed to the plants)				(9,8 % of the total activity fed to the plants)		(5,2 % of the total activity fed to the plants)
overground organs of 31 seedlings 14 days old (experiment plants) fresh weight 5,46 g, dry weight o,28 g	277 5oo	5oo γ	61 4oo	32o γ	9o 2oo	16o γ	41 4oo	8o γ	-
overground organs of 31 seedlings 14 days old (control plants) fresh weight 5,3o g, dry weight o,27 g	-	-	-	22o γ	-	1o γ	-	traces	-
alkaloids built by conversion of hyoscyamine			61 4oo	1oo γ			41 4oo	8o γ	
			(22,1 % of the total activity fed to the plants)				(14,9 % of the total activity fed to the plants)		

As the radioactive hyoscyamine was labelled at the methyl-group the possibility existed that the activity resulted from transmethylation in the plant. Scions of adult Datura stramonium L. which are unable to convert hyoscyamine into hyoscine were fed with ^{14}C labelled hyoscyamine and unlabelled hyoscine. After a week hyoscine without any activity was isolated from these plants.

From this it may be concluded that young aerial shoots of Datura stramonium L. are able to convert hyoscyamine into hyoscine. Alkaloid V, an intermediate product, also appears in this conversion. Further investigations will show whether the roots of Datura stramonium L. are likewise synthesizing hyoscine from hyoscyamine and whether other species of Datura and Atropa bella-donna are similarly able to convert hyoscyamine. Further details concerning synthesis of methyl ^{14}C - hyoscyamine[9] as well as on the isolation of labelled intermediates will be published elsewhere.

---

[9] G. Fodor, G. Janzsó, L. Ötvös and D. Bánfi, Chem. Ber. 93, In press (1960).

Tetrahedron Letters No. 22, pp. 5-6, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

DIE HYDROLYSENGESCHWINDIGKEIT DER GLYKOSIDISCHEN BINDUNGEN IN 4α,6β-BIS-D-GLUCOSIDO-D-GLUCOSE

Almuth Klemer

Organisch-chemisches Institut der Universität Münster (Westf.)

(Received 30 August 1960)

DIE partielle Hydrolyse des Amylopektins ist insbesondere von Wolfrom u. Mitarbeitern[1] eingehend untersucht worden. Dabei wurde unter den Hydrolysenprodukten kein verzweigtes Trisaccharid (4α,6α-Bis-D-glucosido-D-glucose) gefunden. Dies Ergebnis könnte auf eine anomal große Hydrolysengeschwindigkeit der beiden (oder einer) glykosidischen Bindungen (Bindung) hindeuten.

Die Untersuchung der partiellen Hydrolyse von 4α,6β-Bis-D-glucosido-D-glucose[2] als Modellsubstanz zeigt aber, daß beide Bindungen langsamer als die der entsprechenden Disaccharide Maltose und Gentiobiose gespalten werden.

Die Bestimmung (Bedingungen: 100°; 0.05 n H_2SO_4) erfolgte durch die quantitative Ermittlung der Spaltprodukte: D-Glucose, Maltose und Gentiobiose mit Hilfe der Isotopen-Verdünnungsanalyse (^{14}C-D-Glucose u. ^{14}C-Maltose) und der chromatographischen Auftrennung des Hydrolysates an einer Cellulosepulver-Säule.

---

[1] A. Thompson u. M.L. Wolfrom, J. Amer. Chem. Soc. 73, 5849 (1951); dort sind fruhere Arbeiten zitiert.

[2] A. Klemer, Chem. Ber. 92, 218 (1959).

Es wurden zwei unabhängige Versuchsreihen mit je 100 - 150 mg Trisaccharid ausgeführt. Die Hydrolysengeschwindigkeitskonstanten von Maltose und Gentiobiose wurden aus ihren Drehwertsänderungen ermittelt.

Die Rechnung (vergl.)[3] ergibt folgendes:

Die α 1,4-Bindung im Trisaccharid wird ca. 1,5 mal langsamer als Maltose hydrolysiert. Die β 1,6-Bindung im Trisaccharid wird ca. 1,3 mal langsamer als Gentiobiose hydrolysiert.

---

[3] R.W. Jones, R.J. Dimler u. C.E. Rist, J. Amer. Chem. Soc. 77, 1659 (1955).

Tetrahedron Letters No. 22, pp. 7-11, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

PARTIAL SYNTHESIS OF "MIXED-ACID" L-α-LECITHINS

G. H. de Haas and L. L. M. van Deenen.

Laboratory of Organic Chemistry, State University,

Utrecht, The Netherlands

(Received 29 August 1960)

IN a previous paper[1] we have reported the preparation of ten L-α-lecithins, each containing two identical acyl groups, by acylation of L-α-glyceryl-phosphorylcholine. As by-products the corresponding monoacyl derivatives ("lysolecithins") were isolated in rather larger amounts.

If it should be possible to acylate these "lysolecithins" with a different fatty acid, "mixed-acid" L-α-lecithins could be obtained in a way less elaborate than through total synthesis.[2,3] The "lysolecithins" under consideration, however, resisted under various conditions acylation towards the required "mixed-acid" lecithins. Paper chromatography showed that these "lysolecithins" were not identical* with snake venom-formed lysolecithins.

---

* Initially the fatty acid moiety of the "lysolecithins", obtained as by-products, was supposed to be at the γ-position. This wrong assignation was based on the supposed γ-specificity of lecithinase A, which until recently was generally admitted. A definite elucidation of the structure of these "lysolecithins", however, requires further investigation.

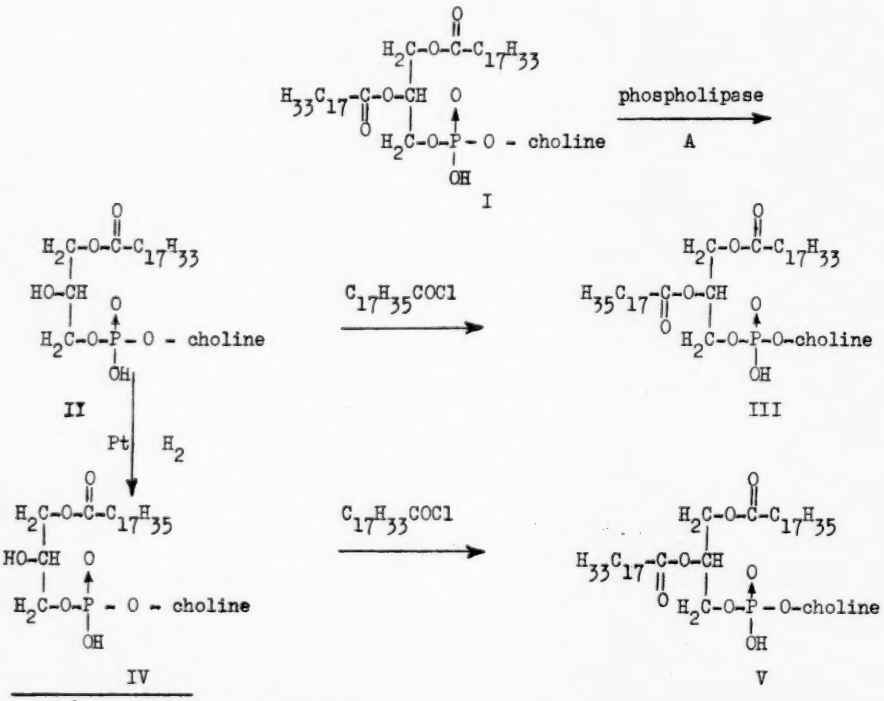
1 F. Kögl ✠, G.H. de Haas and L.L.M. van Deenen, Rec.Trav.Chim. 79, 661 (1960).

2 G.H. de Haas and L.L.M. van Deenen, Tetrahedron Letters No. 9, 1 (1960).

3 G.H. de Haas and L.L.M. van Deenen. Unpublished Work.

Therefore the conversion was tried of lysolecithins prepared by phospholipase A (lecithinase A) degradation of L-α-lecithins containing two identical fatty acids. As demonstrated by degradation experiments on fully synthetic "mixed-acid" L-α-lecithins, lecithinase A liberates only the β-attached fatty acid,[4] thus yielding γ-lysolecithins. Actually upon acylation of these γ-lysolecithins we did obtain "mixed-acid" lecithins in satisfactory yields.

An example is presented of the preparation of the two structural isomeric L-α-lecithins containing one stearic and one oleic acid chain:



[4] G.H. de Haas and L.L.M. van Deenen, Vth Conference on biochemical Problems of Lipids, Marseille, 21-23, July 1960; Cf. also: N.H. Tattrie, J.Lipid.Res. 1, 61 (1959); D.J. Hanahan, H. Brockerhaff and E.J. Barron, J.Biol.Chem. 235, 1917 (1960).

1960

L-α-dioleoyllecithin (I) was prepared according to known methods by acylation of either free L-α-glycerylphosphorylcholine[1] (L-α-GPC) or its amorphous cadmium chloride adduct.[5] Baer and Buchnea[5] pointed out that deacylation of L-α-lecithins with mercuric chloride yields partially racemized L-α-GPC, but that neither racemization nor a migration of the phosphorylcholine moiety occurs during the acylation of synthetic L-α-GPC. Actually in our previous preparation of lecithins[1] using L-α-GPC prepared by mercuric chloride hydrolysis of egg lecithin we obtained lecithins with somewhat too low optical rotations, thus confirming the statements of Baer and Buchnea. Using, however, L-α-glycerylphosphorylcholine prepared by hydrogenolysis of egg lecithin with lithiumaluminium hydride according to the method of Urakami and Okura,[6] optically pure I was obtained (α_D^{20} = + 6.0°; C 9.0 in chloroform). Since lecithinase A does not hydrolyse D-α-lecithins and degradates only the L-isomers to yield the corresponding lysolecithins,[4] it is even possible to prepare by the present method optically pure "mixed-acid" L-α-lecithins starting from optically impure lecithins containing two similar fatty acids.

Degradation of I with snake venom lecithinase A under conditions outlined by Hanahan[7] yielded the corresponding γ-oleoyl-L-α-lysolecithin (II). [Yield: 90-95%; m.p. 240°; α_D^{20} = -3.2°; C 12.0 in chloroform: ethanol (5:1 v/v)]. Analysed as the cadmium chloride adduct. (Found: N 1.64, P 3.65. $(C_{26}H_{54}O_8NP)_2(CdCl_2)_3$ requires N 1.66, P 3.80).

The conversion of this lysolecithin to γ-octadecenoyl-β-octadecanoyl-L-α-lecithin (III) appeared to be possible by acylation of the free product

---

[5] E. Baer and D. Buchnea, Canad.J.Biochem.Physiol. 37, 953 (1959).

[6] C. Urakami and H. Okura, Bull.Chem.Soc.Japan 31, 779 (1958).

[7] D. J. Hanahan, J.Biol.Chem. 195, 199 (1952).

or of the cadmium chloride adduct.

In both cases the crude "mixed-acid" lecithin had to be purified by silica chromatography. Crystallization from chloroform-acetone yielded the wanted lecithin (III) as a colourless, very hygroscopic powder (m.p. 233-235°; α_D^{20} = + 6.0°; C 10.0 in chloroform; yield 43 %, calculated upon the amount of lysolecithin). (Found: C 64.77, H 11.44, N 1.72, P 3.71. $C_{44}H_{88}O_9NP$ requires C 65.39, H 11.22, N 1.73, P 3.83).

For the preparation of the structural isomeric L-α-lecithin (V) II was converted by catalytic hydrogenation (Adams Pt-catalyst) in absolute ethanol into γ-stearoyl-L-α-lysolecithin (IV). (m.p. 235-237°; α_D^{20} = -3.0°; C 5.0 in chloroform-methanol 1:1 v/v; yield 96%). Analysed as the cadmium chloride adduct. (Found: C 38.20, H 7.06, N 1.66, P 3.73. $(C_{26}H_{56}O_8NP)_2(CdCl_2)_3$ requires C 38.23, H 6.91, N 1.71, P. 3.79).

The cadmium chloride adduct of IV was allowed to react with oleoyl chloride according to the method of Baer.[5] After chromatography on silica and crystallization from chloroform-acetone the lecithin (V) was obtained as a colourless, very hygroscopic powder. (m.p. 237°; α_D^{20} = + 6.2°; C 10.0 in chloroform). (Found N 1.81; P 3.97. $C_{44}H_{88}O_9NP$ requires N 1.73, P 3.83).

Both isomeric L-α-lecithins (III and V) were compared using physical and biochemical methods with γ-stearoyl-β-oleoyl-L-α-lecithin obtained by total synthesis.[3] Both isomers exhibit the same molecular orientation at the air/water interface, as demonstrated by the fully identical force-area curves of unimolecular films in the Langmuir-Adams trough. Debye-Scherrer diagrams did not give satisfactory results so far, probably because of lack of crystallinity of these oleic acid containing lecithins

Lecithinase A degradation, however, supplied confirmatory evidence on

the dissimilar position of the fatty acids in both isomers. As in the case of the fully synthetic γ-stearoyl-β-oleoyl-L-α-lecithin, the enzymatic hydrolysis of the lecithin with formula (V) yielded only oleic acid, whereas from the lecithin (III) exclusively stearic acid was released.

This partial synthesis appears to offer vast opportunities for the preparation of many types of "mixed-acid" lecithins, especially those containing highly unsaturated fatty acids. The preparation of other types of phosphatides, e.g. "mixed-acid" cephalins by the outlined procedure, is in progress.

Our thanks are due to Dr. J. Kanters (Laboratory of Crystallography, State University, Utrecht) for X-ray analysis of the described lecithins. The collaboration of Dr. I. Mulder is gratefully acknowledged. We wish to express our gratitude to Dr. J. Tolk and Mr. J. H. van der Maas (Laboratory of Analytical Chemistry, State University, Utrecht) for infra red absorption measurements.

Tetrahedron Letters No. 22, pp. 12-19, 1960. Pergamon Press Ltd. Printed in Great Britain

ION PAIRS, RACEMIZATION, CHLORIDE EXCHANGE AND THE MASS LAW EFFECT IN SOLVOLYSIS OF P-CHLOROBENZHYDRYL CHLORIDE[1]

S. Winstein, Masaru Hojo and S. Smith

Dept. of Chemistry, University of California, Los Angeles, Calif.

(Received 29 August 1960)

In the classic investigations of C. K. Ingold and his coworkers[2], solvolysis of benzhydryl type halides in aqueous acetone was interpreted with the aid of only one variety of carbonium ion intermediate, the dissociated cation, $R^{\oplus}$, as in equation (1). In the so-called mass law effect

$$RCl \underset{k_2}{\overset{k_1}{\rightleftharpoons}} R^{\oplus} + Cl^{\ominus} \qquad R^{\oplus} \xrightarrow{k_3} ROH \qquad (1)$$

(common ion rate depression[3]), chloride ion competes with water for $R^{\oplus}$, diverting it from benzhydrol (ROH) formation back to covalent benzhydryl chloride (RCl). This formulation leads to equation (2) for k_t, the first

$$k_t = \frac{-d(RCl)/dt}{(RCl)} = k_1/[1 + \alpha(Cl^{\ominus})] \qquad (2)$$

order titrimetric rate constant, α denoting (k_2/k_3).

---

[1] Research supported by the National Science Foundation.

[2] C. K. Ingold, et.al., J. Chem. Soc. 979 (1940).

[3] (a) S. Winstein, E. Clippinger, A. H. Fainberg and G. C. Robinson, Chemistry and Industry 664 (1954); (b) S. Winstein, E. Clippinger, A. H. Fainberg, R. Heck and G. C. Robinson, J. Am. Chem. Soc. 78, 328 (1956).

Evaluation of the magnitude of the mass law coefficient, α, is by no means straightforward, since k_1, k_2 and k_3 are all subject to salt effects. Treating the activity coefficients of $R^{\oplus}$ and $Cl^{\ominus}$ by the Debye-Hückel limiting law, that of the transition state in step 1 by an ion-atmosphere theory and those for RCl and the transition state in step 3 as though they remained unity, Hughes and Ingold[2] expressed the dependence of k_t on ionic strength, μ, and common ion concentration, $(Cl^{\ominus})$, in the form of equation (3). In this equation, k_1^o and α^o are values at zero μ

$$k_t = \frac{k_1^o}{10^{\frac{-0.912 \times 10^{16} \gamma \mu}{D^2 T^2}} + \alpha^o(Cl^{\ominus})\ 10^{\frac{-1.815 \times 10^6 \mu^{1/2}}{(DT)^{3/2}}}} \qquad (3)$$

and γ is a parameter related to the polarity of the transition state in step 1. Not only does equation (3) specify a logarithmic fit of salt effects in solvolysis, but it makes no provision for specificity of salt effects. The assessments of the mass law effect by Ingold[2] or Kohnstam[4] with equation (3) or with equation (2) at constant μ inevitably involve the assumption that the "ionic strength" effect of the common ion salt, e.g., HCl or NaCl, is the same as that of some non-common ion salt.

In his original formulation[2], Ingold did not consider ion pair intermediates in the solvolysis scheme. Even after such intervention of ion pair intermediates in solvolysis of other systems was recognized[5], the same formulation was continued[6]. On the other hand, Kohnstam[4], who

---

[4] (a) B. Bensley and G. Kohnstam, J. Chem. Soc. 3408 (1955); (b) G. Kohnstam and B. Shillaker, ibid. 1915 (1959).

[5] W. G. Young, S. Winstein and H. L. Goering, J. Am. Chem. Soc. 73 1958 (1951).

[6] (a) O. T. Benfey, E. D. Hughes and C. K. Ingold, J. Chem. Soc. 2488 (1952); (b) A. R. Hawdon, E. D. Hughes and C. K. Ingold, ibid. 2499 (1952).

has more recently interpreted the hydrolysis of diphenyldichloromethane in aqueous acetone on the basis of equations (1)-(3), concluded that his results would be consistent with intervention of ion pair intermediates if ROH arises only from dissociated $R^{\oplus}$. More insight into such matters can be provided by an optically active benzhydryl halide[7], and we have now measured rates of racemization, acid formation and radio-chloride exchange of p-chlorobenzhydryl chloride in 80% acetone. These show that it is important to distinguish between ionization and dissociation[3,5] and to recognize explicitly the intervention of ion pair intermediates[3,5] in solvolysis of benzhydryl halides even in solvents as dissociating as 80% acetone.

Optically active p-chlorobenzhydryl chloride was available from the action of hydrogen chloride on the p-chlorobenzhydrol in pentane[8] at -80°, this material being several times as active as the product of the reaction of carbinol with thionyl chloride[7a]. Fairly satisfactory first order rate constants for disappearance of optical activity, k_α, are obtained at 25° with ca. 0.1 M solutions of active RCl in 80% aqueous acetone with or without added lithium chloride or perchlorate (Table I and Fig. 1). The rotation of the final solution of chlorobenzhydrol is zero within experimental error.

First order titrimetric rate constants, k_t, for 0.01 M solutions of RCl are steady within a run. As illustrated in Table II and Fig. 1, k_t is increased by non-common ion salts and decreased by common ion salts. At an RCl concentration of 0.1 M, corresponding to the polarimetric work, k_t values are slightly lower than those at 0.01 M (Table I). They are still

---

[7] (a) S. Winstein and J. S. Gall, Tetrahedron Letters 2, 31 (1960); (b) S. Winstein, J. S. Gall, M. Hojo and S. Smith, J. Am. Chem. Soc. 82, 1410 (1960).

[8] P. G. Stevens and N. L. McNiven, J. Am. Chem. Soc. 61, 1295 (1939).

Table I

Rate Constants for 0.10 M RCl in 80% Acetone at 25.0°

Salt	Concn. 10^2M	10^5k_a Sec.$^{-1}$	10^5k_t Sec.$^{-1}$	10^4k_{e2} M^{-1}Sec.$^{-1}$	$10^5k_t^u$ Sec.$^{-1}$
-	-	5.7 ± 0.3	2.31 ± 0.02	-	2.6
LiCl	1.02		2.34 ± 0.02	1.10 ± 0.03	2.7
LiCl	5.4		2.15 ± 0.02	0.97 ± 0.04	2.9
LiCl	9.0		1.97 ± 0.02	0.97 ± 0.02	3.1
LiCl	10.0	5.7 ± 0.2	1.94 ± 0.03		3.1
$LiClO_4$	5.0	6.8 ± 0.5			
$LiClO_4$	10.0	8.0 ± 0.4			

Table II

k_t Values for 0.010 M RCl in 80% Acetone at 25.0°

Salt	Concn. 10^2 M	10^5k_t Sec.$^{-1}$	Salt	Concn. 10^2 M	10^5k_t Sec.$^{-1}$
-	-	2.45 ± 0.02	Bu_4NBr	4.98	2.62 ± 0.03
LiCl	5.09	2.33 ± 0.02	Bu_4NBr	10.0	2.61 ± 0.03
LiCl	10.3	2.08 ± 0.02	$LiClO_4$	5.14	2.98 ± 0.02
Bu_4NCl	4.95	2.18 ± 0.05	$LiClO_4$	9.82	3.35 ± 0.02
Bu_4NCl	9.21	1.81 ± 0.02	LiBr	1.02	2.64 ± 0.03
Bu_4NClO_4	5.00	2.55 ± 0.01	LiBr	5.00	2.94 ± 0.01
Bu_4NClO_4	10.0	2.54 ± 0.01	LiBr	10.0	3.25 ± 0.01

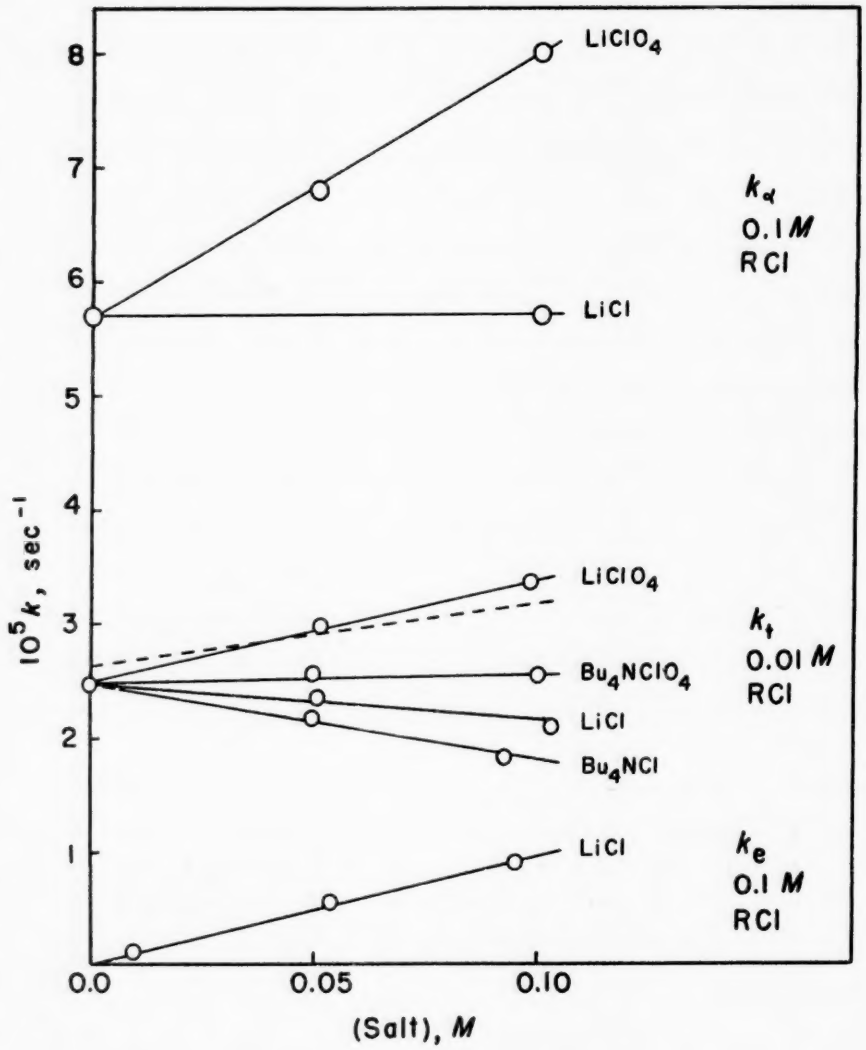


Fig. 1.- Effects of salts on k_α, k_t, and k_e.

quite steady in a run, acceleration of rate by accumulating electrolyte balancing common ion rate depression. The observed polarimetric rate constants are obviously 2.5 - 3 times as large as the titrimetric values[9].

With the pattern of salt effects on k_t as it is, it is difficult to assess what contribution the mass law effect makes to the gap between k_α and k_t without calling on independent evidence. It is evident from Table II and Fig. 1 that equation (3) fails to fit the observed pattern of salt effects on k_t. Instead of different non-common ion salts giving identical accelerated k_t values and different common ion salts leading to identical depressed rates, the observed effects depend on the salt. The specificity is especially marked for the change of cation from lithium to tetrabutylammonium. As pointed out previously[10], equation (3) was insufficiently tested, and it has become increasingly clear that there is very considerable specificity of salt effects on the various solvolysis steps even in solvents of relatively high dielectric constant[10,11]. Other recent evidence of such specificity pertains to t-butyl chloride hydrolysis in water[12] as solvent, ionization of neophyl and 3-phenyl-2-butyl toluenesulfonates in 50% dioxane[13] and α values in hydrolysis of trityl chloride in aqueous dioxane[14].

---

[9] An erroneous preliminary (k_α/k_t) ratio of 4.9 was previously mentioned[7b].

[10] A. H. Fainberg and S. Winstein, J. Am. Chem. Soc. 78, 2763 (1956).

[11] (a) G. R. Lucas and L. P. Hammett, J. Am. Chem. Soc. 64, 1928 (1942); (b) O. T. Benfey, E. D. Hughes and C. K. Ingold, J. Chem. Soc. 2494 (1952); (c) F. Spieth and A. R. Olson, J. Am. Chem. Soc. 77, 1412 (1955).

[12] G. A. Clarke, R. W. Taft, Jr., and T. R. Williams, Page 8R of Abstracts of American Chemical Society Meeting, Boston, Mass., April 5-10, 1959.

[13] E. F. J. Duynstee, E. Grunwald and M. L. Kaplan, J. Am. Chem. Soc. in press.

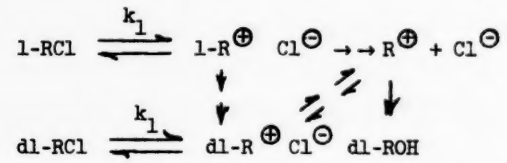
[14] Y. Pocker, Chemistry and Industry 1599 (1957).

Independent evidence regarding the magnitude of the mass law effect or common ion rate depression is the rate of radio-chloride exchange accompanying hydrolysis of p-chlorobenzhydryl chloride. Second order rate constants[15] (k_{e2}) for such exchange accompanying hydrolysis of 0.1 M RCl are fairly constant within a run, and these are summarized in Table I. Since external ion return is inevitably associated with exchange[3], $k_{e2}(Cl^{\ominus})$, the first order rate constant for radio-chloride exchange at the prevailing chloride ion concentration, represents an upper limit to the decrease in k_t due to common ion rate depression. The reason that it is an upper limit is that exchange can also be visualized by way of undissociated ion pairs, and such exchange is not associated with common ion rate depression. Addition of $k_{e2}(Cl^{\ominus})$ to the observed k_t should yield an upper limit to the k_t value, k_t^u, which would be observed if external ion return and the corresponding common ion rate depression were absent. Table I lists these k_t^u values for 0.1 M RCl, $k_{e2}(Cl^{\ominus})$ being calculated for $(Cl^{\ominus})$ equal to the value at one polarimetric half-life of the optically active RCl. In Fig. 1 are plotted these k_t^u values as a dashed line, as well as initial first order radio-chloride exchange rate constants, k_e.

It is evident that the maximum correction for external ion return still leaves k_a twice as great as k_t^u. It is clear that ion pair intermediates play an important role in solvolysis of p-chlorobenzhydryl chloride even in 80% aqueous acetone. The minimum required elaboration of the solvolysis scheme is the following:

---

[15] E. R. Swart and L. J. le Roux, J. Chem. Soc. 2110 (1956).



In this scheme, solvolysis product is shown arising from dissociated $R^{\oplus}$ and not ion pairs, but it is really not clear that no variety of ion pair intermediate leads to product. At least for intimate ion pairs, it seems more likely that they do not lead to carbinol than that they do lead to this product which is, however, completely racemic.

With I denoting the fraction of ion pair intermediates which undergo ion pair return and R being the fraction which become racemic, equation (4) expresses the relation between k_1, k_α and k_t^u. A minimum value of I

$$k_\alpha - k_t^u = k_1 IR \qquad (4)$$

may be obtained by setting R equal to unity, this in turn making k_α equal to k_1. On this basis I has values of 0.46 - 0.54, at least half of the ion pair intermediates from ionization of RCl undergoing ion pair return. I may be considerably larger than the estimated minimum value since it seems very probable that R is substantially less than unity, much ion pair return occurring with retention of configuration of RCl.

The present work has disclosed that k_α for a benzhydryl chloride exceeds k_t or k_e, not only in acetic acid[7b] (D = 6) and acetone [7a] (D = 20.7), but even in 80% acetone (D = 29.6). Apparently, this is true also for the two non-hydroxylic solvents, sulfur dioxide[16] (D = 14) and nitromethane[16] (D = 36.7).

---

[16] Unpublished work of Hughes, Ingold, Pocker and Swedlund, quoted by Y. Pocker, Trans. Faraday Soc. 55, 1266 (1959).

Tetrahedron Letters No. 22, pp. 20-22, 1960. Pergamon Press Ltd. Printed in Great Britain

THE REACTION OF ORGANOLITHIUM REAGENTS WITH PERFLUOROVINYL DERIVATIVES OF TIN AND SILICON.

Dietmar Seyferth, Tadashi Wada[1] and Gunter Raab

Department of Chemistry

Massachusetts Institute of Technology

Cambridge, Massachusetts, U.S.A.

(Received 23 August 1960)

It is known that phenyllithium undergoes nucleophilic addition to the olefinic double bond of triphenylvinylsilane to give, after hydrolysis, β-phenylethyltriphenylsilane.[2] The reaction of phenyllithium with triphenylvinyltin, on the other hand, is one of exchange, in which tetraphenyltin and vinyllithium are formed.[3]

We have investigated the action of organolithium reagents on perfluorovinyl derivatives of silicon and tin and have obtained very similar results, viz., an addition reaction with perfluorovinylsilanes and an exchange reaction with perfluorovinyltin compounds which gives the new perfluorovinyllithium reagent, CF_2=CFLi.

The reaction between triethylperfluorovinylsilane[4] and organolithium

---

[1] On leave from the Shin-Etsu Chemical Industry Co., Ltd., Tokyo, Japan.

[2] L.F. Cason and H.G. Brooks, J. Amer. Chem. Soc. 74 4582 (1952); J. Org. Chem. 19, 1278 (1954).

[3] D. Seyferth and M.A. Weiner, Chem. and Ind. (London) 402 (1959).

[4] D. Seyferth, K.A. Brändle and G. Raab, Angew. Chem. 72, 77(1960).

reagents in ether solution resembles that of lithium compounds with tetrafluoroethylene[5]: the adduct formed loses lithium fluoride, producing a new fluoroolefin. This reaction is a general one which usually results

$$Et_3SiCF{=}CF_2 \xrightarrow{RLi} Et_3SiCFLiCF_2R \xrightarrow{-LiF} Et_3SiCF{=}CFR$$

in good yields of silyl-substituted fluoroolefins. The action of phenyllithium, vinyllithium, allyllithium and n-butyllithium on triethylperfluorovinylsilane gave α,β-difluoro-β-triethylsilylstyrene (b.p. 91°/0.55 mm.; n_D^{25} 1.5113); 1,2-difluoro-1-triethylsilyl-1,3-butadiene (b.p. 43-4°/0.9 mm.; n_D^{25} 1.4562); 1,2-difluoro-1-triethylsilyl-1,4-pentadiene (b.p. 51°/1.6 mm.; n_D^{25} 1.4382); and 1,2-difluoro-1-triethylsilyl-1-hexene (b.p. 53°/0.4 mm.; n_D^{25} 1.4309). respectively.

A reaction between phenyllithium and triphenylperfluorovinyltin[4] carried out in diethyl ether at room temperature resulted in precipitation of tetraphenyltin in good yield, but no evidence could be obtained for the presence of perfluorovinyllithium in the dark brown, opaque solution. However, it was found that perfluorovinyllithium is stable in ether at low temperature. Thus addition of three equivalents of ethereal phenyllithium to 0.023 mole of phenyl-tris(perfluorovinyl)tin in ether at -35° to -40° resulted in instantaneous precipitation of tetraphenyltin (97% isolated yield) and formation of a dark solution. Addition of triethyltin chloride (0.0684 mole), dissolved in ether, was followed by slow warming to room temperature, filtration, treatment of the filtrate with potassium fluoride solution (to remove unreacted Et_3SnCl as the insoluble fluoride) and

---

[5] S. Dixon, J. Org. Chem. 21, 400(1956).

fractional distillation. Triethylperfluorovinyltin[4] was obtained in 40% yield. A similar exchange reaction between n-butyllithium and n-butyl-tris(perfluorovinyl)tin could be effected in pentane. However, in this solvent exchange is not complete, and it was found best to use the lithium reagent and the tin compound in 2:1 molar ratio. When the perfluorovinyllithium preparation was carried out at -30° and triethyltin chloride used to characterize the lithium reagent formed, the work-up procedure described above gave triethylperfluorovinyltin in 46-50% yield. The stability of perfluorovinyllithium is greater in pentane than in ether. The reagent appeared to be stable in pentane at 0°, but short refluxing of its pentane solution destroyed it completely. The reactions of perfluorovinyllithium are under investigation.

An analogous difference in behavior of perfluorovinylsilicon and -tin compounds toward Grignard reagents in ether solution was noted. Similar behavior also was observed with more conventional nucleophiles. While

$$Et_3SiCF{=}CF_2 + C_6H_5MgBr \longrightarrow Et_3SiCF{=}CFC_6H_5 + MgBrF$$

$$(C_6H_5)_3SnCF{=}CF_2 + C_6H_5MgBr \longrightarrow (C_6H_5)_4Sn + CF_2{=}CFMgBr$$

alcoholic sodium ethoxide caused complete cleavage of the perfluorovinyl group in tri-n-butylperfluorovinyltin[4], giving tri-n-butyltin ethoxide (b.p. 115°/0.1 mm.), the reaction of this reagent with triethylperfluorovinylsilane gave the addition-elimination product, $Et_3SiCF{=}CFOEt$ (b.p. 47.5°/0.9 mm.; n_D^{25} 1.4252), in 28% yield, as well as triethylethoxysilane in 69% yield.

Acknowledgments. This work was supported by the U.S. Army Quartermaster Research and Engineering Command (Chemicals and Plastics Division, Chemical Products Branch) and by the U.S. Air Force under Contract No. AF 33(616)-7124, monitored by the Materials Laboratory, Wright Air Development Division, Wright-Patterson Air Force Base, Ohio.

Tetrahedron Letters No. 22, pp. 23-28, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

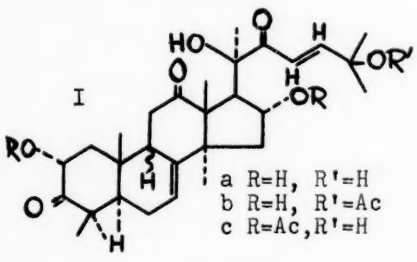
THE STEREOCHEMISTRY OF THE CUCURBITACINS[1,2]

David Lavie, Youval Shvo and Otto Richard Gottlieb[3]

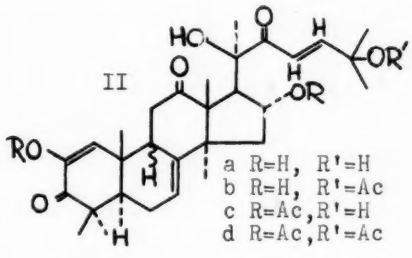
Daniel Sieff Research Institute, the Weizmann Institute of Science, Rehovoth, Israel

(Received 16 August 1960)

THE stereochemistry of ring A of some of the cucurbitacins has been discussed in a previous communication.[4] We wish to report now the experiments which led us to present most of the stereochemistry of the four naturally occurring cucurbitacins: elatericin A (Ia), cucurbitacin B (Ib), elatericin B (IIa) and elaterin (IIb), leaving only the configuration of C-9 undeter-



a R=H, R'=H
b R=H, R'=Ac
c R=Ac, R'=H



a R=H, R'=H
b R=H, R'=Ac
c R=Ac, R'=H
d R=Ac, R'=Ac

---

[1] This investigation was supported by a research grant CY-2810 (C3) from the National Cancer Institute of the National Institutes of Health, U.S. Public Health Service.

[2] This communication is part XVII in the series: The Constituents of Ecballium elaterium L., part XVI. D. Lavie and O.R. Gottlieb, J.Amer.Chem.Soc. in the press.

[3] On leave of absence from the Instituto de Química Agrícola, Ministério da Agricultura, Rio de Janeiro, Brazil.

[4] D.Lavie and O.R.Gottlieb, Chem.& Ind. 929 (1960).

mined.

The configuration of the hydroxyl group at C-2 in elatericin A and cucurbitacin B, as well as in the tetrahydro-derivatives of elatericin B and elaterin has been previously presented assuming that rings A/B are trans fused.[4] That this junction is indeed trans is indicated by the fact that, in the substances possessing a diosphenol system, as for example IIa and IIb, the hydrogen reducing the double bond in ring A approaches the molecule from the rear, while in the corresponding enol acetates IIc and IId it proceeds from the front. In substances with an A/B cis junction the rear of ring A is highly hindered and only one type of product, resulting from frontal attack, should be obtained. The A/B rings junction being trans, the hydrogen at C-5 is α by convention, while the methyl group at C-10 is β-oriented.

The stereochemistry of the C-16 hydroxyl will now be presented. It is known that the molecular rotation shifts resulting from acetylation of a C-16 hydroxyl group in steroids are of opposite signs for α or β-orientation, the former being negative ($\Delta[M]_D$ -239°), while the latter is positive ($\Delta[M]_D$ +64°).[5] The observed difference between elatericin B diacetate (IIc, $[M]_D$ -492°) and elatericin B (IIa, $[M]_D$ -267°)[6] is -225°. This value is in agreement with an α-oriented hydroxyl at C-16 in the cucurbitacins, since only acetylation at this position

---

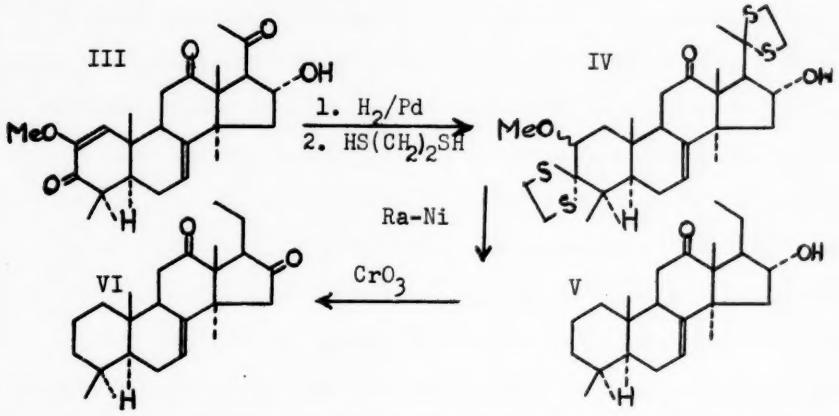
[5] L.F. Fieser and M. Fieser, Steroids p. 179, Reinhold Publishing Corporation, New York (1959).

[6] D. Lavie and D. Willner, J.Amer.Chem.Soc. 80, 710 (1958).

1960

contributes to the optical rotation difference, the acetate at C-2 being enolic.

The stereochemistry of the C/D rings junction was determined using molecular rotation difference between a C-16 ketone and the corresponding secondary alcohol in substances VI and V. These substances, without oxygenated groups in the side chain, were chosen to reduce possible vicinal effects. They were prepared from III[7] by the following reaction sequence:



It is noteworthy that during treatment with Raney nickel of the ethylenedithioketal IV concomitant hydrogenolysis of the 2-methoxy group occurred with the expected desulfurisations, to yield the monohydroxy derivative V, m.p. 169-170°, $[\alpha]_D$+ 182° (c 0.93).[¥] Oxydation of V with chromium trioxide yielded

---

[7] D. Lavie and D. Willner, J.Amer.Chem.Soc. 82, 1668 (1960).

[¥] Melting points were taken on a Kofler hot-stage microscope and optical rotation measurements were carried out in chloroform solution.

the diketone VI, m.p. 185-187°. $[\alpha]_D$+55° (c 1.19). The molecular rotation difference between VI and V is -457°, which is in agreement with the computed $\Delta[M]_D$(CO-CHOH)-439°. This value was calculated from $\Delta[M]_D$(CO)-498°[8] and $\Delta[M]_D$(CHOH)-59°[5] given for functional groups at C-16 in similar ring systems with 13β, 14α-substituents. It can be deduced, therefore, that this is the orientation which does occur in the cucurbitacins.

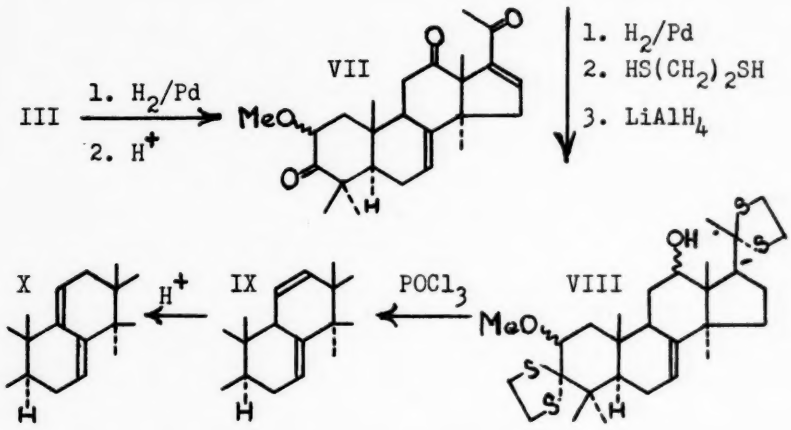
At this point we can present evidence indicating the orientation of the side chain at C-17 in the cucurbitacins. It was found that the carbonyl group at C-22 could not be induced to form a hemiketal with the 16-hydroxyl upon heating with acid. Such cyclisations have been observed to occur readily under these conditions when the side chain at C-17 and the vicinal hydroxyl at C-16 are cis.[9] It can be deduced therefore, that these substituents are on opposite sides of the cucurbitacin ring system and, since the C-16 hydroxyl was found to be α, the side chain must be β-oriented.

In accordance with the foregoing observations, the cucurbitacins belong to the lanostane type triterpenes. This conclusion was confirmed by the preparation of the heteroanular diene, X, obtained by the following sequence of reactions :

---

[8] A. Bowers, T.G. Halsall, E.R.H. Jones and A.J. Lemin, J.Chem.Soc. 2548 (1953).

[9] St. Kaufmann and G. Rosenkranz, J.Amer.Chem.Soc. 70, 3503 (1948).



The ultraviolet spectrum of X, λ_{max} 236, 244 and 251 mμ, is characteristic of 7,9(11)-dienes in the lanostane series. Analogous conjugated dienes in the euphane series exhibit maxima displaced to shorter wavelength.[10]

Finally we should like to present an argument favouring the configuration at C-20 as shown in I and II. It has been previously observed that the side chain cleavage with periodic acid is much slower in elatericin A diacetate (Ic), than in elatericin A (Ia).[11] This would indicate that the site of attack of the hydroxy-ketone becomes masked upon acetylation of the C-16 hydroxyl, while the opposite direction still does not leave free access to the oxidising agent. Inspection of

---

[10] M.C. Dawson, T.G. Halsall and R.E.H. Swayne, J.Chem. Soc. 590 (1953).

[11] D. Lavie and Y. Shvo, J.Amer.Chem.Soc. 82, 966 (1960).

a model indicated that such a possibility occurs when the methyl group at C-20 is directed towards the rear of the molecule. The stereochemistry at C-20 should be therefore as in lanostane by replacing the 20β-H with OH.[12]

With these observations in mind, we propose hereby the following structures for the four cucurbitacins investigated: 2α,16α,20,25-tetrahydroxy-3,12,22-trioxo-(9ξ-H)-lanosta-7, 23-trans-diene for elatericin A (Ia), 2α,16α,20-trihydroxy-25-acetoxy-3,12,22-trioxo-(9ξ H)-lanosta-7,23-trans-diene for cucurbitacin B (Ib), 2,16α,20,25-tetrahydroxy-3,12,22-trioxo-(9ξH)-lanosta-1,7,23-trans-triene for elatericin B (IIa) and 2,16α,20-trihydroxy-25-acetoxy-3,12,22-trioxo-(9ξH)-lanosta-1,7,23-trans-triene for elaterin (IIb).

One of the authors (O.R.G.) gratefully acknowledges support from the Conselho Nacional de Pesquisas, Brazil.

---

[12] For the nomenclature used see: S.Allard and G.Ourisson, Tetrahedron 1, 277 (1957).

Tetrahedron Letters No. 22, pp. 29-32, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

REARRANGEMENTS OF OXO-DICYCLOPENTADIENES

R.C. Cookson, J. Hudec and R.O. Williams

The University, Southampton.

(Received 2 Sebtember 1960)

IN the account[1] of their beautiful experiments on the rearrangement of asymmetric hydroxydicyclopentadienes, Woodward and Katz mentioned that Oppenauer oxidation of the syn-8-alcohol (I) in boiling benzene yielded the 1-ketone (II). This observation suggested to us either that the thermal isomerisation of the 8-ketone (III) was much faster than that of the alcohols (which are stable in boiling benzene), or that it was catalysed by the electrophilic aluminium t-butoxide.

We have now prepared the 8-ketone (III), m.p. 63-64° (with rearrangement to the 1-ketone), ν_{max} 1780 cm $^{-1}$, λ_{max} 278 mμ, ε 25, by oxidation of the alcohol (I) with chromic oxide in pyridine. It is stable in the crystalline state or in solution in cyclohexane at 20°, but a trace of boron trifluoride in the cyclohexane causes rapid rearrangement to the 1-ketone (II). Hydrogen chloride also strongly catalyses

---

[1] R.B. Woodward and T.J. Katz, Tetrahedron 5, 70 (1959).

the rearrangement in dioxan at room temperature. In fact it proceeds slowly even in neutral ethanol at 20°.

The equilibrium lies entirely on the side of the 1-ketone (II) probably because of a combination of the greater strain associated with a trigonal than with a tetrahedral atom at C-8[2] and the conjugation in the 1-ketone (II). The much faster rearrangement of the 8-ketone than of the 8-alcohol, especially in polar solvents, is understandable in terms of the transition state leading to Woodward and Katz's intermediate (IV), which in this case will have considerable dipolar character. The catalysis by Lewis and proton acids, and even by hydrogen-bonding solvents, is also to be expected from consideration of the polarised transition state leading to (IV): the essential bond-breaking is symbolised in formula (V) (which omits for simplicity the other electronic and nuclear displacements, already discussed for the general case by Woodward and Katz). Yates and Eaton[3] have recently described catalysis of the rearrangement of the tetrachloro-derivative of (III) by aluminium chloride. The apparently greater sensitivity to acid of the 8-ketone (III) than of its tetrachloro-derivative[3] may be partly due to the greater basicity of its carbonyl group.

---

[2] W.G. Woods, R.A. Carboni and J.D. Roberts, J. Amer. Chem. Soc. 78, 5653 (1956).

3 P. Yates and P. Eaton, Tetrahedron Letters No. 11, 5 (1960).

1960

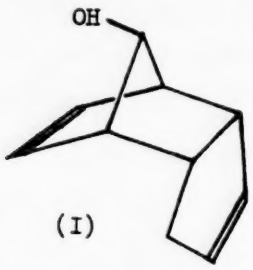
Ultraviolet irradiation of the 1-ketone (II) gave the isomer (VI), m.p. 124-126°, ν_{max} 1760 cm $^{-1}$, λ_{max} 297 mμ, ε 13. The symmetry of the cage (VI) is such that its cracking amounts to a simple competition (in this particular system) between the ability of an α-carbonyl and an α-methylene group to promote cleavage of a cyclobutane ring.

In our flow apparatus the cage was stable up to 425°, but at 450° it underwent clean pyrolysis. No product could be detected that was not also present in the pyrolysate of the 1- and 8-ketones, so that the cage must crack only in the two ways that simultaneously break two cyclobutane rings (horizontal planes in VI), not in either direction that initially breaks only one cyclobutane ring (vertical planes in VI). Cyclopentadiene and dihydroindene[4] (VII) were formed in all cases, characterised, inter alia, by their respective adducts with benzoquinone, m.p. 73-74°, and maleic anhydride, m.p. 142-143°. The ratio of the areas of the peaks for cyclopentadiene and dihydroindene on gas chromatograms of the pyrolysates from the 1-ketone (II), the cage (VI) and the 8-ketone (III) were respectively 1 : 1.7, 1 : 3.7 and 1 : 5.85. Clearly at high temperatures in the absence of acid and in the gas phase the 8-ketone (III) loses carbon monoxide faster than it rearranges to the 1-ketone (II). The cage shows no tendency

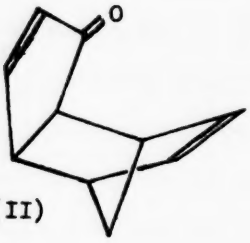
---

[4] K. Alder and F.H. Flock, Ber. 87, 1916 (1954).

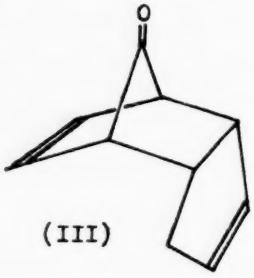
to break next the carbonyl group (to give II) in preference to the methylene group (to give III).



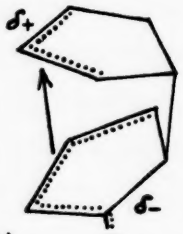
(I)



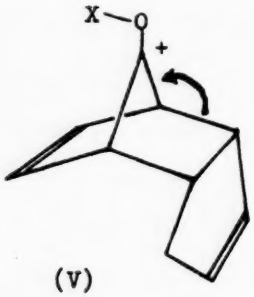
(II)



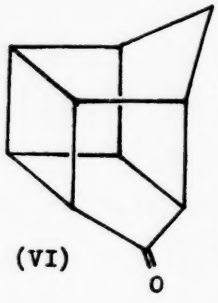
(III)



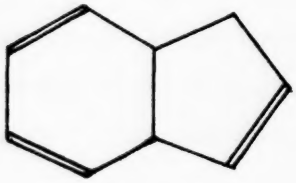
(IV)



(V)



(VI)



(VII)

Tetrahedron Letters No. 22, pp. 33-37, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

ABSOLUTE CONFIGURATION OF GUAIOL

Ken'ichi Takeda and Hitoshi Minato

Research Laboratory, Shionogi & Co. Ltd., Osaka, Japan

(Received 5 September 1960)

RECENTLY, Djerassi's group*[1] presented evidence on the absolute configuration of the methyl group at C-4 in guaiol (I) from the identity of bis-homonepetalinic acid and its derivative (III) having the known configurations at C-1, C-4 and C-5 in guaiol, with the degradation product of dextrorotatory dihydroguaiol (II). They also assumed tentatively the β** configuration of the C-10 methyl group in guaiol from the results of the rotatory dispersion curve of the indanone derivative (V) derived from the above-mentioned dibasic acid (III). Later, Šorm's group[2] reported on the absolute configuration of the C-10 position from

---

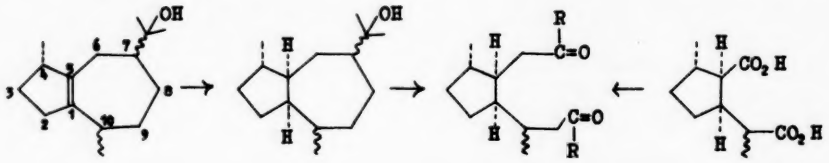
* We are very much indebted to Dr. Carl Djerassi (Stanford University) for sending us the manuscript of the paper "On the absolute configuration of guaiol. Correlation with Nepetalinic Acid" before publication.

1 E. J. Eisenbraun, T. George, B. Riniker and C. Djerassi, J. Amer. Chem. Soc. 82 (1960), in press.

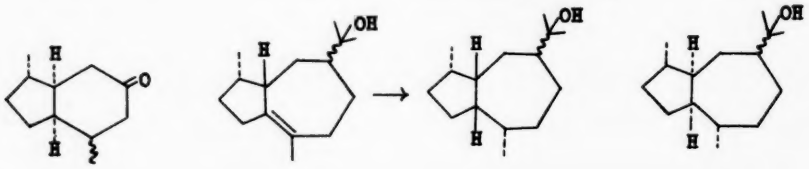
2 L. Dolejs, A. Mironov and F. Šorm, Tetrahedron Letters No. 11, 18 (1960).

** The terms "α" and "β" are used according to the steroidal convention.

the structural elucidation of levorotatory dihydroguaiol (VIIa) obtained from bulnesol (VI).



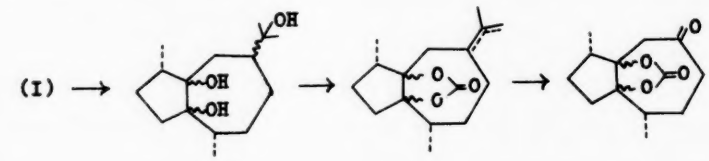
(I) (II) (III) R=OH or NH_2 (IV)



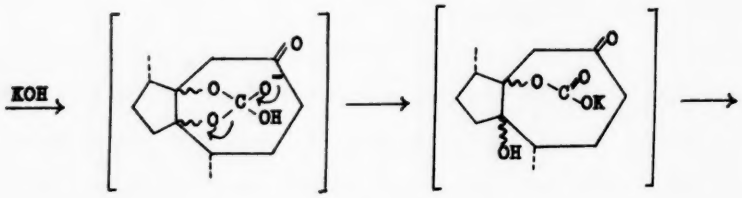
(V) (VI) (VIIa) (VIIb)

We now wish to report our results on the same problems by other routes.

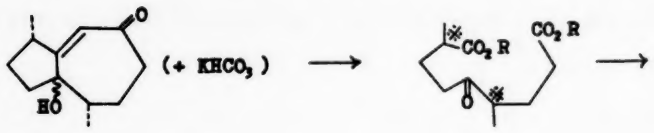
In the course of our attempted investigation on the synthesis of linderazulene[3] from guaiol, we obtained an α,β-unsaturated ketone (XI) by the following route:



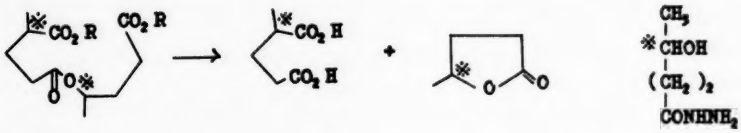
(VIII) (IX) (X)



[3] K. Takeda and W. Nagata, Pharm. Bull. 1, 164 (1953).



(XI) (XII)



(XIII) (XIV) (XV) (XVI)

The identical triol (VIII), m.p. 106-107°, $[\alpha]_D^{24}$ -7°, I.R. ν_{max}^{Nujol} 3385 (OH), 1010 cm^{-1} (C-O), was obtained from guaiol either by the action of OsO_4 or by $KMnO_4$ oxidation. Treatment of this triol with phosgen easily afforded a mixture of unsaturated dioxycarbonyl compounds (IX), I.R. ν_{max}^{Nujol} 1796 (C=O), 1648 cm^{-1} (C=C), dehydration of the hydroxyl group in the side chain having occurred simultaneously. This mixture was converted without purification to a ketone (X), m.p. 113-114°, $[\alpha]_D^{21}$ +2.9°, I.R. ν_{max}^{Nujol} 1784, 1716 cm^{-1} (C=O), 2,4-dinitrophenylhydrazone, m.p. 241-243°, in ca 60% yield by ozonolysis. When this ketone was treated with 1 mol. KOH at room temperature for 3 hrs. in ethanol solution, filtration produced 94% of potassium hydrogencarbonate within 15 minutes, while the α,β-unsaturated ketone (XI), m.p. 47-49°, $[\alpha]_D^{28}$ +176.7°, U.V. $\lambda_{max}^{alcohol}$ 237.5 mμ (ε 9620), I.R. ν_{max}^{Nujol} 3445 (O-H), 1641 (C=O), 1603 cm^{-1} (C=C), was obtained from the filtrate in excellent yield. Although KOH was used in this case (the reaction proceeding most likely through the intermediates as shown in the flow-sheet), there probably occurred no epimerisation at C-4. Ozonolysis of the α,β-unsaturated ketone (XI) in ethyl acetate followed

by hydrogen peroxide oxidation in a neutral medium afforded an oily ketodibasic acid (XII R=H).

Its dimethyl ester (XII R=CH_3), b.p. 134°/1.5 mm., $[\alpha]_D^{24}$ +17.1°, I.R. ν_{max}^{Nujol} 1740, 1713 cm^{-1} (C=O), obtained by the action of CH_2N_2, was converted to the ester (XIII), b.p. 139°/2.5 mm., $[\alpha]_D^{21}$ +16.7°, I.R. ν_{max}^{Nujol} 1740 cm^{-1} (C=O), by the Baeyer-Villiger reaction.[4] As this reaction is accompanied by retention of cinfiguration of the migrating group[5] it was concluded that the C-10 methyl group kept its original configuration.

The thus obtained ester (XIII) was saponified by potassium carbonate in methanol to yield α-methylglutaric acid (XIV) as well as γ-methylbutyrolactone (XV).

α-Methylglutaric acid (XIV), m.p. 85-86°, obtained from this ester showed a positive rotatory power, $[\alpha]_D^{13}$ +17.9°, and was identical with the synthetic (+)-α-methylglutaric acid, m.p. 82-84°, $[\alpha]_D^{19}$ +15.4°.[6]

On the other hand, γ-methylbutyrolactone (XV) thus obtained showed b.p. 99-100°/23 mm., $[\alpha]_D^{23}$ -35.1°, and its infrared spectrum (film) was identical with that of synthetic (-)-γ-methylbutyrolactone,[7] b.p. 97-98°/22 mm., $[\alpha]_D^{23}$ -17.2°. Furthermore, the hydrazide (XVI) of this lactone derived from guaiol, m.p. 91.5-92.5°, $[\alpha]_D^{22}$ +16.6° was also identical in all respects (mixture melting point determination and infrared comparison) with the hydrazide of the synthetic (-)-lactone, m.p. 90-91°, $[\alpha]_D^{24}$ +19.0°.

---

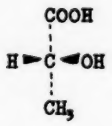
[4] W. D. Emmons and G. B. Lucas, J. Amer. Chem. Soc. 77, 2287 (1955).

[5] R. B. Turner, ibid. 72, 878 (1950).

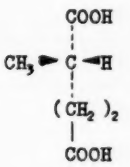
[6] E. Berner and R. Leonardsen, Liebigs Ann. 538, 1 (1939).

[7] P. A. Levene and H. L. Haller, J. Biol. Chem. 69, 165 (1926).

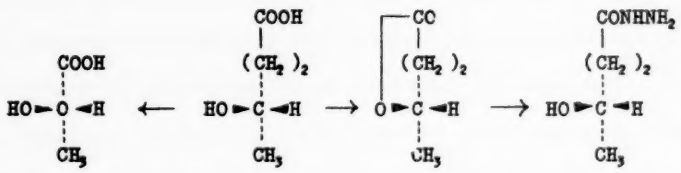
Since S-(+)-α-methylglutaric acid was correlated with R-(-)-lactic acid by A. Fredga[8] and S-(-)-γ-methylbutyrolactone with S-(+)-lactic acid by P. A. Levene[7,9] as shown in the chart, the C-4 and the C-10 methyl groups in guaiol both possess the α-configuration. Guaiol, levorotatory (m.p. 79°) and dextrorotatory dihydroguaiol (oil) should therefore be represented by XVII, VIIa and VIIb, respectively.



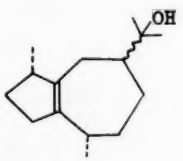
R-(-)-Lactic Acid



S-(+)-α-Methylglutaric Acid



S-(+)-Lactic Acid S-(-)-γ-Methylbutyrolactone



(XVII)

---

[8] A. Fredga, Arkiv. Kemi. Mineral Geol. 24A, No. 32 (1947); E. J. Eisenbraun and S. M. McElvain, J. Amer. Chem. Soc. 77, 3383 (1955).

[9] P. A. Levene and H. L. Haller, J. Biol. Chem. 77, 555 (1928).

Tetrahedron Letters No. 22, pp. 38-44, 1960. Pergamon Press Ltd. Printed in Great Britain

19-HYDROXY-10-ISOTESTOSTERONE

Franz Sondheimer, Raphael Mechoulam and Milon Sprecher

Daniel Sieff Research Institute, Weizmann Institute of Science, Rehovoth, Israel

(Received 14 September 1960)

WE wish to report the synthesis of 19-hydroxy-10-isotestosterone (XVII), the first example of a steroid hormone analog in which the 10-position, but no other asymmetric center, is inverted. This type of compound is of interest in view of the recent announcement that certain steroid hormone analogs in which both the 9- and the 10-positions are inverted possess interesting biological properties.[1]

19-Nor-Δ^4-androstene-3,17-dione (I)[2] on ozonolysis

---

[1] E.H. Reerink, H.F.L. Schöler, P. Westerhof, A. Querido, A.A.H. Kassenaar, E. Diczfalusy and K.C. Tillinger, Nature 186, 168 (1960); P. Westerhof and E.H. Reerink, Rec. Trav. Chim. 79, 771, 794 (1960).

[2] A.L. Wilds and N.A. Nelson, J. Amer. Chem. Soc. 75, 5366 (1953); C. Djerassi, L. Miramontes, G. Rosenkranz and F. Sondheimer, J. Amer. Chem. Soc. 76, 4092 (1954).

1960

and subsequent oxidation with hydrogen peroxide[3] yielded the diketo-acid (II) [m.p. 179-181°; $[\alpha]_D$ + 72° (all rotations in chloroform). Found : C, 70.00; H, 8.01]. Esterification with diazomethane produced the corresponding methyl ester which with ethylene glycol and p-toluenesulfonic acid in boiling benzene gave the diketal (III) (m.p. 117-119°; $[\alpha]_D$ - 2°. Found : C, 66.67; H, 8.88). The latter was then subjected to a Barbier-Wieland degradation through treatment with phenylmagnesium bromide to yield the diphenyl-carbinol (IV) (m.p. 145-146°; $[\alpha]_D$ + 45°. Found : C, 76.13; H, 8.28), followed by boiling aqueous acetic acid and oxidation of the resulting diketo-diphenyl-ethylene (V) λ_{max}^{EtOH} 250 mμ, ε 16,200) with ruthenium tetroxide and sodium periodate in aqueous acetone.[4] The nor-diketo-acid (VI) (m.p. 190-192°; $[\alpha]_D$ + 63°. Found : C, 69.25; H, 8.15) thus obtained appears to exist in the acid form (I.R. bands at 1730 and 1705 cm^{-1}), unlike an analogous nor-keto-acid in the 19-methyl series which exists as the lactol.[5]

---

[3] See R.B. Turner, J. Amer. Chem. Soc. 72, 579 (1950); A.J. Birch, Chem. and Ind. 616 (1951); J.A. Hartman, A.J. Tomasewski and A.S. Dreiding, J. Amer. Chem. Soc. 78, 5662 (1956).

[4] S. Sarel and Y. Yanuka, J. Org. Chem. 24, 2018 (1959) and references quoted there.

[5] F.L. Weisenborn, D.C. Remy and T.L. Jacobs, J. Amer. Chem. Soc. 76, 552 (1954).

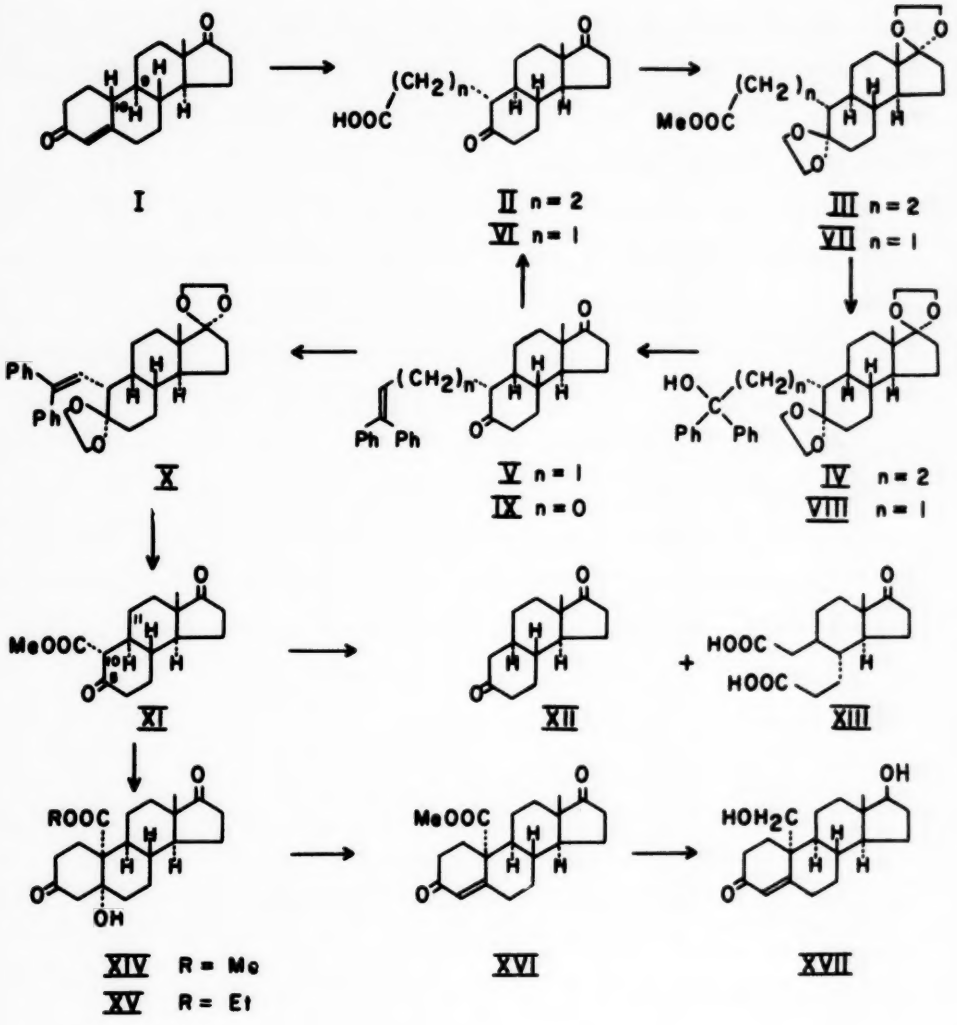
The sequence which had led from the diketo-acid (II) to the diphenyl-ethylene (V) was then repeated with the nor-diketo-acid (VI) and yielded successively the corresponding methyl ester (m.p. 99-100°; $[\alpha]_D$ + 66°. Found : C, 69.62; H, 8.01), the diketal (VII) (m.p. 143-145°; $[\alpha]_D$ - 2°. Found : C, 65.99; H, 8.45), the diphenyl-carbinol (VIII) (m.p. 139-140°; $[\alpha]_D$ + 99°. Found : C, 76.46; H, 8.04) and the diphenyl-ethylene (IX) (m.p. 197-200°; $[\alpha]_D$ + 213°; λ_{max}^{EtOH} 250 mμ, ε 18,100. Found : C, 84.27; H, 7.67). Ethylene glycol and p-toluenesulfonic acid in boiling benzene converted (IX) to the diketal (X) (m.p. 194-195°; $[\alpha]_D$ + 83°; λ_{max}^{EtOH} 250 mμ, ε 18,600. Found : C, 78.61; H, 7.89), the double bond of which was cleaved by the ruthenium tetroxide method.[4] Esterification of the product with diazomethane and subsequent cleavage of the ketal groupings with aqueous sulfuric acid in boiling methanol produced the dinor-diketo-ester (XI) (m.p. 148-150°; $[\alpha]_D$ + 77°. Found : C, 69.14; H, 7.96).

It is of interest that the β-keto-ester (XI) is not enolic (I.R. bands at 1730 and 1705 cm^{-1} but no hydroxyl band; no color with ferric chloride; no reaction with acetic anhydride and pyridine), doubtlessly due to the $\Delta^{5(10)}$-trans (B/C)-system (steroid numbering) being energetically unfavored[6] and because of steric interaction in the enol between the carbomethoxy group

---

[6] See R.B. Turner, W.R. Meador and R.E. Winkler, J. Amer. Chem. Soc. 79, 4122 (1957).

1960


I
II n = 2
VI n = 1
III n = 2
VII n = 1
IV n = 2
VIII n = 1
V n = 1
IX n = 0
X
XI
XII
XIII
XIV R = Me
XV R = Et
XVI
XVII

and the 11α-hydrogen atom.[7] Nevertheless, saponification with potassium hydroxide in boiling methanol resulted in the decarboxylated diketone (XII) (dioxime : m.p. 202-204°. Found : N, 11.11) besides the dicarboxylic acid (XIII) [m.p. 159-161°; $[\alpha]_D$ + 92° (dioxane). Found : C, 63.68; H, 7.90].

Michael reaction of the β-keto-ester (XI) with methyl vinyl ketone in ethanolic sodium ethoxide at 0-20° led to the ketol methyl ester (XIV) (m.p. 171-173.5°; $[\alpha]_D$ + 39°. Found : C, 68.80; H, 8.27) and the corresponding ethyl ester (XV) (m.p. 122-124°; $[\alpha]_D$ + 36°. Found : C, 69.77; H, 8.27) as the only crystalline products isolated.[8] The methyl ester (XIV) on dehydration with p-toluenesulfonic acid in boiling benzene yielded the unsaturated ketone (XVI) (m.p. 146-148°; $[\alpha]_D$ - 164°; λ_{max}^{EtOH} 242 mμ, ε 14,100. Found : C, 72.76; H, 7.92), which must possess the assigned carbon skeleton since 19-nor-Δ^4-androstene-3,17-dione (I) was obtained smoothly on saponification with boiling methanolic potassium hydroxide.

---

[7] For similar cases, see P.A. Stadler, A. Nechvatal, A.J. Frey and A. Eschenmoser, Helv. Chim. Acta 40, 1373 (1957); N.A. Nelson and R.N. Schut, J. Amer. Chem. Soc. 80, 6630 (1958); E. Wenkert and B.G. Jackson, J. Amer. Chem. Soc. 81, 5601 (1959).

[8] Experiments which point to the ketol structures (XIV) and (XV) rather than to the alternative bridged-ring formulations (W.S. Johnson, J.J. Korst, R.A. Clement and J. Dutta, J. Amer. Chem. Soc. 82, 614 (1960)) will be reported in the full paper.

1960

Finally (XVI) was reduced with lithium aluminum hydride in boiling tetrahydrofuran and the product re-oxidized with manganese dioxide in chloroform,[9] whereby 19-hydroxy-10-isotestosterone (XVII) [m.p. 199.5-201°; $[\alpha]_D$ - 215°; λ_{max}^{EtOH} 244-249 mμ (plateau), ε 13,800. Found : C, 75.17; H, 9.42] was formed. The identical compound resulted when the ketol ethyl ester (XV) was subjected to the same reaction sequence as described for the methyl ester (XIV). The 10-iso formulation for (XVII) follows from the optical rotatory dispersion curve (negative multiple Cotton effect; to be discussed in the full paper) and the non-identity with 19-hydroxytestosterone ($[\alpha]_D$ + 110°).[10] The unusual U.V. spectrum of (XVII) is presumably due to interaction between the 19-hydroxy and the Δ^4-3-ketone groupings, since the corresponding diacetate showed a normal spectrum (λ_{max}^{EtOH} 239 mμ).

All the compounds described showed I.R. spectra compatible with the assigned structures.

---

[9] Method of F. Sondheimer, C. Amendolla and G. Rosenkranz, J. Amer. Chem. Soc. 75, 5930 (1953).

[10] M. Ehrenstein and K. Otto, J. Org. Chem. 24, 2006 (1959).

Acknowledgments. We are indebted to the U.S. National Institutes of Health for a research grant (No. H-2476), to Syntex S.A. (Mexico City) for a gift of 19-nor-Δ^4-androstene-3,17-dione, to Prof. W.S. Johnson (University of Wisconsin) for providing some model ketols, to Dr. M. Ehrenstein (University of Pennsylvania) for a sample of 19-hydroxytestosterone and to Prof. C. Djerassi (Stanford University) for the rotatory dispersion determinations.

1960

19

Tetrahedron Letters No. 23, pp. 1-4, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

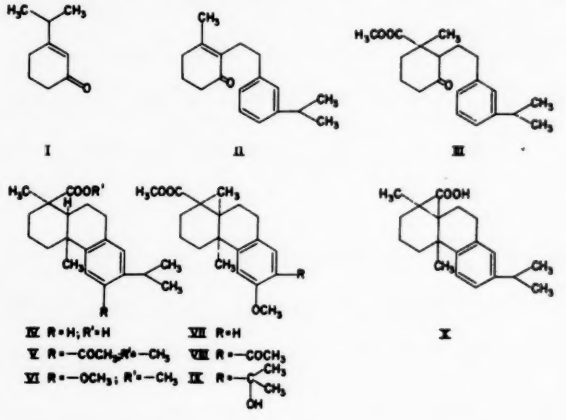
SYNTHESIS OF TWO STEREO-ISOMERS OF DEHYDROABIETIC ACID

Moheswar Sharma

Department of Organic Chemistry, Indian Association for the Cultivation of Science. Jadavpur, Calcutta-32

(Received 27 September 1960)

THE condensation product from 3-keto-4-methylpentenyl chloride and ethyl acetoacetate was hydrolysed with a mixture of acetic and sulphuric acid, leading to the formation of m-isopropylcyclohexenone (I, red 2:4-dinitrophenylhydrazone, m.p. 155°. Found: C, 56.3; H, 5.7; N, 17.6. $C_{15}H_{18}O_4N_4$ requires C. 56.6; H, 5.7: N. 17.6). The ketone (I) was condensed with ethyl bromoacetate to afford a doubly unsaturated ester (b.p. 128°/0.6 mm; Found: C, 75.1; H, 9.3. $C_{13}H_{20}O_2$ requires C, 75.0; H, 9.6). This was dehydrogenated with sulphur (b.p. 105-110°/ 4 mm; Found: C, 75.5; H, 8.6. $C_{13}H_{18}O_2$ requires C, 75.7; H, 8.7). The ester so obtained, was reduced with lithium-aluminium-



hydride to afford m-isopropylphenethyl alcohol[1] (b.p. 95-100°/ 4 mm; Found: C, 79.9; H, 9.7. $C_{13}H_{16}O$ requires C, 80.4; H, 9.8). The condensation product from the corresponding bromide with Hagemann's ester in the presence of potassium-t-butoxide afforded on alkaline hydrolysis the unsaturated ketone[2] (II) in a good yield. This was boiled with an ethanolic solution of potassium cyanide[3] and the crude condensation product was subjected to alkaline hydrolysis. The acidic product so obtained, was esterified with an excess of diazomethane to afford the keto-ester (III) (b.p. 195°/0.4 mm: Found: C, 75.5; H, 8.7. $C_{20}H_{28}O_3$ requires C, 75.9; H, 8.9; yellow 2:4-dinitrophenylhydrazone, m.p. 151°; Found: C, 62.8; H, 6.3; N, 11.7. $C_{26}H_{32}O_6N_4$ requires C, 62.9; H, 6.4; N, 11.3). The keto-ester (III) was condensed with methylmagnesium-iodide and the crude carbinol was dehydrated by boiling with oxalic acid in toluene. The product was found to be a mixture of the corresponding unsaturated ester and the related γ-lactone (5.677). The unsaturated ester was cyclised with polyphosphoric acid[4] and the neutral and acidic products were separated. The acidic material was again separated into two definite individuals (I) m.p. 202° (Found: C, 80.1; H, 9.4. $C_{20}H_{28}O_2$ requires C, 80.0; H, 9.4; Methyl ester, m.p. 98°; found: C, 79.7; H, 9.5. $C_{21}H_{30}O_2$ requires C, 80.2; H, 9.6) and (ii) m.p. 155° (Found: C, 80.3; H, 9.7. $C_{20}H_{30}O_2$ requires C, 80.0; H, 9.4; methyl ester, m.p. 62°; Found: C, 80.5; H, 9.4. $C_{21}H_{30}O_2$ requires C, 80.2; H, 9.6). The

---

[1] R.D. Hawarth and R.L. Barker, J. Chem. Soc. 1299 (1939).

[2] G. Stork and A. Burgstahler, J. Amer. Chem. Soc. 73, 3544 (1951).

[3] U.R. Ghatak, D.K. Datta and S.C. Ray, J. Amer. Chem. Soc. 82, 1728 (1960).

[4] F.E. King, T.J. King and J.G. Topliss, Chem. & Ind. 113 (1956).

ester melting at 98° afforded a mono-keto ester[5] on oxidation with chromic acid (orange-red 2:4-dinitrophenylhydrazone, m.p. 200°; Found: C, 64.1; H, 6.2; N, 10.8. $C_{27}H_{32}O_6N_4$ requires C, 64.3; H, 6.3; N, 11.1). From the rate of hydrolysis and formation of the mono-keto ester mentioned above, the acid melting at 202[2] is represented by the stereoformula (IV).

The above methyl ester m.p. 98° was allowed to react with acetylchloride in the presence of aluminium chloride to afford the ketone (V), m.p. 141° (λ_{max}^{alc} 257 mμ; log ε 3.9; Found: C, 77.4; H, 8.8. $C_{23}H_{32}O_3$ requires C, 77.5; H, 9.0. orange 2:4-dinitrophenylhydrazone, m.p. 214°, Found: C, 64.8; H, 6.8. $C_{29}H_{36}O_6N_4$ requires C, 64.9; H, 6.7). The keto ester (V) was allowed to react with excess of perbenzoic acid[6] in chloroform and the crude product thus obtained, on alkaline hydrolysis and subsequent treatment with excess of diazomethane afforded (VI) m.p. 130-131° (Found: C, 76.4; H, 9.6. $C_{22}H_{32}O_2$ requires C, 76.6; H, 9.4). With a view to preparing an authentic sample of (VI), methyl o-methylpodocarpate[7] was condensed with acetyl chloride in the presence of aluminium chloride. The ketone (VIII, m.p. 124°; Found: C, 73.4; H, 8.3. $C_{21}H_{28}O_4$ requires C, 73.2; H, 8.1. Orange 2:4-dinitrophenylhydrazone, m.p. 265°; Found: C, 61.9; H, 6.3; $C_{27}H_{32}O_7N_4$ requires C, 61.8; H, 6.1) was treated with methylmagnesium-iodide to afford the carbinol (IX), m.p. 148° (Found: C, 73.5; H, 8.9. $C_{22}H_{32}O_4$ requires C, 73.3; H, 8.9). This was dehydrated by heating with glacial acetic acid and the unsaturated compound, on catalytic hydrogenation afforded an ester, m.p. 130-131° alone or mixed with (VI).

---

[5] E. Wenkert and B.G. Jackson, J. Amer. Chem. Soc. 80, 211 (1958).

[6] E. Wenkert and B.G. Jackson, J. Amer. Chem. Soc. 80, 217 (1958).

[7] R.K. Bhattacharyya, J. Indian Chem. Soc. 22, 165 (1945).

The acid melting at 155° is most probably represented by the stereoformula (X) as belonging to the cis-series. This followed from detailed studies with the four stereo-isomers[3] of the desisopropyl acid, although the cis-locking could not be definitely established through the formation of di-keto-ester.[5]

The author is indebted to Professor P.C. Dutta and to Dr. U.R. Ghatak for their kind interest and valuable suggestions during this work. Grateful thanks are also due to Mrs. Chhabi Dutta and Mr. A.B. Dutta of this laboratory for analyses.

Tetrahedron Letters No. 23, pp. 5-7, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

THE FORMATION OF DODECAPHENYLCYCLOHEXASILANE FROM THE REACTION OF DICHLORODIPHENYLSILANE WITH SODIUM AND WITH LITHIUM

H. Gilman, D. J. Peterson, A. W. Jarvie and H. J. S. Winkler

Chemistry Department, Iowa State University,

Ames, Iowa

(Received 19 September 1960)

FROM the reaction of dichlorodiphenylsilane with sodium, Kipping and co-workers[1] obtained by careful fractionation of the very complex mixture of products a substance called Compound (B). They designated this compound as octaphenylcyclotetrasilane. It was recently reported[2] that their Compound (A) was octaphenylcyclotetrasilane and not a compound containing "two tervalent silicon atoms". There was a high degree of reasonableness at that time for such a structure in view of some uncommon reactions. We have now found that their Compound (B) is dodecaphenylcyclohexasilane. We prepared Compound (B) by the action of sodium or lithium on dichlorodiphenylsilane and showed this compound to be identical with a sample of the original compound prepared many years ago.

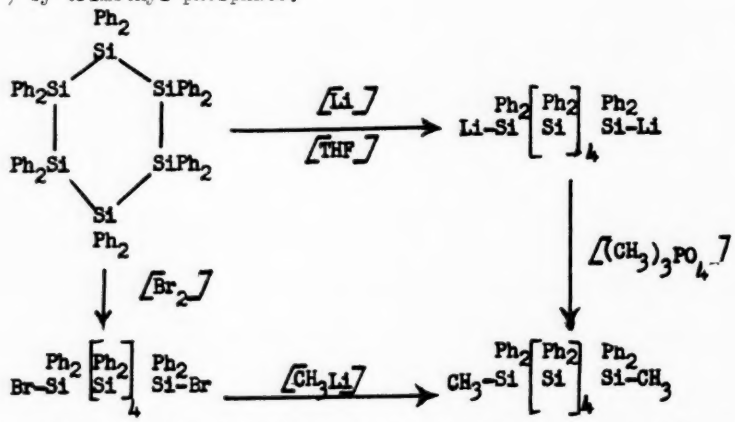
The structure of Compound (B) was established by two different types

---

[1] F.S. Kipping and J.E. Sands, J. Chem. Soc. 119, 830, 848 (1921); F.S. Kipping, Ibid. 123, 2590 and 2598 (1923); F.S. Kipping, Ibid. 125, 2291 (1924); F.S. Kipping, Ibid. 2719 and 2728 (1927); F.S. Kipping and H.E. Murray, Ibid. 360 (1929); A.R. Steele and F.S. Kipping, Ibid. 2545 (1929); F.S. Kipping, Proc. Roy. Soc. A 159, 139 (1937).

[2] H. Gilman, D.J. Peterson, A.W. Jarvie and H.J.S. Winkler, J. Amer. Chem. Soc. 82, 2076 (1960).

of cleavage reactions. One of these involved cleavage by lithium metal in tetrahydrofuran to give 1,6-dilithiododecaphenylhexasilane. This dilithium compound was characterized by a quantitative determination of its silyllithium content and by its conversion to 1,6-dimethyldodecaphenylhexasilane (m.p. 183-184°) by trimethyl phosphate.



This compound was shown to be identical with the product obtained by first cleaving Compound (B) by one mole equivalent of bromine in benzene to give 1,6-dibromododecaphenylhexasilane (m.p. 204-206°), and then reacting this dibromo compound with methyllithium. The dimethyl derivative obtained by these two routes were shown to be identical by the method of mixed melting points and the superimposability of their infrared spectra.

(Found: C, 78.97, 79.05, 79.14, 79.23; H, 5.75, 5.68, 5.72, 5.81; Si, 14.90, 15.21. Calc. for $CH_3[Si(C_6H_5)_2]_6CH_3$, ($C_{74}H_{66}Si_6$): C, 79.1; H, 5.88; Si, 14.93.) Hydrogen value (moist piperidine). (Found: 102, 96. Calc. 100) Mol. Wt. (in perylene) (Found: 1170, 1110. Calc.: 1123.)

(Found: C, 78.72, 78.91; H, 5.30, 5.45; Si, 15.37, 15.27. Calc. for $[Si(C_6H_5)_2]_6$, ($C_{72}H_{60}Si_6$): C, 79.07; H, 5.53; Si, 15.40.) Hydrogen value. (Found: 125, 124. Calc.: 123.) Mol. Wt.: (in perylene). (Found: 1115, 1070.

Calc.: 1094.) Mol. Wt. (by isothermal distillation). (Found: 1225, 1200, 1025.)

Acknowledgments - The authors are grateful to Dr. F. B. Kipping for supplying us with a sample of Compound (B) which belonged to the original collection of Dr. F. S. Kipping. This research was supported in part by the United States Air Force under contract AF 33(616)-3510 monitored by Materials Laboratory, Directorate of Laboratories, Wright Air Development Center, Wright-Patterson AFB, Ohio.

1960

Tetrahedron Letters No. 23, pp. 8-10, 1960. Pergamon Press Ltd. Printed in Great Britain

NEW HETERAROMATIC COMPOUNDS CONTAINING TWO BORON ATOMS

S. S. Chissick, M. J. S. Dewar[1] and P. M. Maitlis[2]

Department of Chemistry, Queen Mary College,

Mile End Road, London, E.1.

(Received 22 September 1960)

THE preparation of 10:9-borazarophenanthrene and of 10:9 boroxarophenanthrene by Friedel-Crafts cyclizations of 2-biphenylylaminoboron dichlorides and of 2-biphenylyloxyboron dichloride in presence of aluminium chloride, and of 2:1-borazaronaphthalenes by condensation of o-aminostyrene with boron trichloride or phenylboron dichloride have been described.[3,4,5] We wish to report the first two examples of analogous bis-borazaro compounds formed by analogous double cyclizations from diamines.

Phenylboron dichloride (6 g) in dry benzene (20 ml) was added to 2:6-diaminodiphenyl (2.5 g) in dry benzene (250 ml) over 45 min at room temperature. A white precipitate of the complex separated which redissolved on heating. After boiling under reflux for 1 hr, almost two moles of hydrogen chloride

---

[1] Present address: Department of Chemistry, University of Chicago, Chicago 37, Illinois.

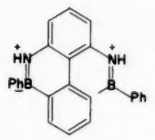
[2] Present address: Department of Chemistry, Cornell University, Ithaca, New York.

[3] M. J. S. Dewar, Ved P. Kubba and R. Pettit, J. Chem. Soc. 3073 (1958).

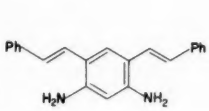
[4] M. J. S. Dewar and R. Dietz, J. Chem. Soc. 1344 (1960).

[5] M. J. S. Dewar and R. Dietz, J. Chem. Soc. 2728 (1959).

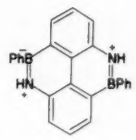
had been evolved. The solution was evaporated and the residue heated for 1 hr at 170° with a catalytic amount of aluminum chloride. The cold reaction product was hydrolyzed with wet benzene and chromatographed from ether on alumina. This gave 4:10-diphenyl-4:10-dibora-5:9-diazapyrene (I) (1.0 g, 21%), m.p. 200-2° (Found: C, 81.2; H, 5.4; N, 7.9; B, 6.0; M.W. (Rast) 348. $C_{24}H_{18}N_2B_2$ requires C, 80.9; H, 5.1; N, 7.9; B. 6.0; M.W. 356). The I.R. spectrum showed only a single NH peak, indicating that cyclization had occurred. The U.V. spectrum in ethanol was quite unlike that of the parent diphenyl, showing peaks at 258 mμ (log ε, 4,5) and 277 mμ (log ε, 4.0) and a broad shoulder at 335 mμ (log ε, 3.7).



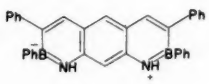
I



II



IV



III

When 1:3-diamino-4:6-bis(8-styryl)benzene (II) was heated with two moles of phenylboron dichloride in benzene, two moles of hydrogen chloride were evolved but no further reaction took place and no boron-containing product could be isolated. (These conditions sufficed for the synthesis of 2-phenyl-2:1-borazaronaphthalene from o-aminostyrene).[5] However use of tetralin led to evolution of almost four moles of hydrogen chloride during 2 hr reflux and formation of 2:3:6:7-tetraphenyl-2:7-dibora-1:8-diazaanthracene (III), m.p. 270°, which was isolated in 94% yield by removing the tetralin under reduced pressure and crystallizing the residue first from moist benzene and then from dry benzene (Found: C, 84.1; H, 5.4; N, 6.0; B, 4.4. $C_{34}H_{28}N_2B_2$

requires: C, 84.1; H, 5.8; N, 5.8; B, 4.5%). The molecular weight could not be measured either in camphor or in naphthalene. The I.R. and U.V. spectra were consistent with the structure (III).

We also tried to make the isomer (IV) of (I) by reacting 2:2'-diaminodiphenyl with boron trichloride or phenylboron dichloride and treating the condensation products with aluminum chloride; in this case no cyclization took place. Presumably the positively charged nitrogen in an arylaminoboron dichloride deactivates the adjacent ring; consequently both rings are deactivated in the bis-aminoboron dichloride derived from 2:2'-diaminophenyl and cyclization cannot therefore take place.

The authors wish to thank British Petroleum Ltd. for the award of a Fellowship (to P.M.M.) and the Department of Scientific and Industrial Research for the award of a Studentship (to S.S.C.).

Tetrahedron Letters No. 23, pp. 11-13, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

SYNTHESIS OF THE THIAPYRYLIUM CATION

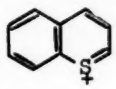
R. Pettit

Department of Chemistry, University of Texas, Austin, Texas

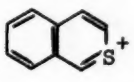
(Received 6 September 1960)

According to current concepts the tropylium, pyridinium, pyrylium and thiapyrylium cations (I, X = CH = CH, NH, O and S respectively) should all possess enhanced stability because of the presence of a sextet of delocalised π electrons occupying low energy molecular orbitals associated with the cationic system. Of these ions, only salts of the thiapyrylium cation remain to be isolated. The stability of this cation can, however, be anticipated following the isolation of salts of various alkyl and aryl substituted thiapyrylium cation,[1] from mass spectral studies of alkylated thiophenes[2] and, more recently, from the isolation of salts of the two possible benz-derivatives (II) and (III).[3]

I



II



III

We now wish to report the isolation of several salts of the parent, unsubstituted cation (I, X = S). The synthetic route we have used is similar to that employed by Dewar and Pettit for the synthesis of tropylium salts[4] and is outlined in the following scheme.

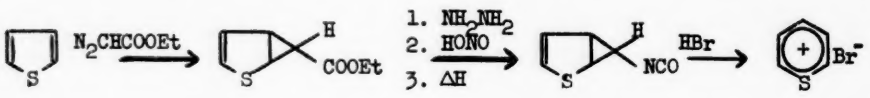
---

[1] R. Wizinger and P. Ulrich, Helv. Chim. Acta 39, 207 (1956).

[2] V. Hanus and V. Cermak, Coll. Czech. Chem. Comm. 24, 1602 (1959).

[3] A. Lüttringhaus and N. Engelhard, Chem. Ber. 93, 1525 (1960).

[4] M. J. S. Dewar and R. Pettit, J. Chem. Soc. 2021 (1956).



IV V

The product (IV) of the reaction between thiophene and diazoacetic ester was converted to the isocyanate (V) in the manner indicated above. Treatment of the isocyanate in nitromethane with hydrogen chloride followed by addition of ether afforded cyanuric acid and thiapyrylium chloride. Thiapyrylium bromide was prepared in a similar manner using hydrogen bromide. The chloride and bromide salts are solids, insoluble in nonpolar solvents but readily soluble in polar solvents, especially water. Thiapyrylium iodide was obtained as a crystalline solid following addition of sodium iodide to an aqueous solution of thiapyrylium bromide. The perchlorate, and chloroplatinate salts were obtained in the same manner.

It is interesting that the chloride, bromide and iodide salts of thiapyrylium are white, yellow and orange respectively. This same type of charge transfer spectra is also shown with the corresponding salts of the tropylium cation.

It is also interesting to note that whereas pyrylium perchlorate apparently is readily decomposed in water,[5] thiapyrylium iodide on the other hand is best recrystallised from hot water, indicating a greater stability of the latter cation. Of course, the thiapyrylium cation is attacked by stronger nucleophiles such as OH^- and CN^-; the products of these reactions are being studied further and will be reported at a later date.

Preparation of thiapyrylium iodide. The ester (II)[6] (10 g) was heated with hydrazine (35 cc of 85 g) and alcohol (60 cc) for four hours. The alcohol was removed under reduced pressure and, on cooling the residue,

---

[5] F. Klages and H. Träger, Chem. Ber. 86, 1327 (1953).

[6] Prepared through a modified procedure of W. Steinkopf and H. Augestad - Jensen. Leibigs Ann. 428, 154 (1922).

the hydrazide was obtained as white needles (6.0 g) m.p. 166°. (Found: C, 46.13; H, 5.11; N, 17.70; S, 20.53. $C_6H_8N_2OS$ requires: C, 46.13; H, 5.16; N, 17.94; S, 20.53).

At 0° a solution of sodium nitrite (1.0 g) was added with stirring to a solution of the hydrazide (2.0 g) in acetic acid (25 cc), water (10 cc) and benzene (10 cc). After fifteen minutes more benzene (40 cc) was added, the mixture then filtered and the benzene layer separated, washed with sodium carbonate and dried over sodium sulfate. The benzene solution was heated at reflux for 1 1/4 hours and the solvent then carefully removed under reduced pressure. The residue of isocyanate V was immediately dissolved in dry nitromethane (20 cc) and, while kept cold, the solution was saturated with hydrogen bromide. Anhydrous ether was added to the mixture and the yellow precipitate then collected and dissolved in water (20 cc). The aqueous solution was filtered and the filtrate added to a saturated aqueous solution of sodium iodide. Thiapyrylium iodide separated as orange-red needles (0.9 g), m.p. 209° (dec.). (Found: C, 26.65; H, 2.13; S, 14.04; I, 56.35. C_5H_5SI requires: C, 26.80; H, 2.25; S, 14.31; I, 56.63).

Acknowledgement The author gratefully acknowledges support from the Robert A. Welch Foundation.

Tetrahedron Letters No. 23, pp. 14-17, 1960. Pergamon Press Ltd. Printed in Great Britain

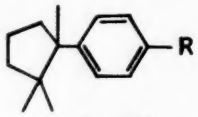
CUPARENE AND CUPRENENE

Tetsuo Nozoe and Hitoshi Takeshita

Dept. of Chemistry, Tohoku University, Sendai, Japan

(Received 2 October 1960)

IN 1958, Erdtman et al.[1] isolated two sesquiterpenic hydrocarbons, widdrene and widdrene II, from heartwood of Chamaecyparis thujoides, Biota orientalis and various Widdringtonia, the former being identical with Thujopsene.[2] Widdrene II contains about 60% of an aromatic hydrocarbon named cuparene, whose structure was elucidated by Enzell and Erdtman[3] to be new ring system of sesquiterpene (A:R=Me). The present investigation



A R = CH_3
R = COOH

concerned with the isolation of its biogenetic precursor, dihydrocuparene, to which we name cuprenene, and with the synthesis of dl-cuparene.

Neutral part of the essential oil from Thujopsis dolabrata Sieb. et Zucc. contains thujopsene, b.p. 123°/12 mm, $[\alpha]_D^{26}$ -106.4°, as a major component but,

---

1 H. Erdtman and B. R. Thomas, Acta Chem. Scand., 12, 267 (1958).

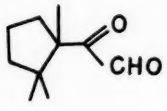
2 H. Erdtman and T. Norin, ibid., 13, 1124 (1959).

3 C. Enzell and H. Erdtman, Tetrahedron, 4, 361 (1958).

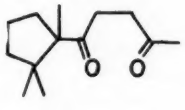
in fractional distillation, decrease of the absolute value of $[\alpha]_D$ was observed to reach a fraction (I) of b.p. 132/12 mm, $[\alpha]_D^{26}$ +63.8°, n_D^{26} 1.5112 d_4^{25} 0.9283, toward the end of thujopsene fraction. The fraction (I),[4] λ_{max}^{MeOH} 265 mμ (log ε 3.41), absorbs 2 molar equivalents of hydrogen (Pd in Ethanol) and 1.2 mole of bromine (vigorous evolution of hydrogen bromide was observed).

Heating of (I) with chloranil or selenium dioxide gave colorless oil (II), b.p. 131/12 mm, n_D^{26} 1.5195, $[\alpha]_D^{26}$ +64.0°, d_4^{25} 0.9350, IR spectrum of which is completely identical with that of cuparene reported by Erdtman.[3] That the fraction (I) is closely related with cuparene is confirmed by oxidation studies. Nitric acid oxidation of (I) gave terephthalic acid and cuparenic acid (III) (A:R=COOH)[3], m.p. 163°(S-p-Bromobenzylthiouronium salt, $C_{23}H_{29}O_2N_2SBr$, m.p. 187°. p-Bromophenacyl ester, $C_{23}H_{25}O_3Br$, m.p. 125°), whereas ozonolysis (175°) afforded, besides oxalic acid and formaldehyde, d-camphonanic acid (IV), m.p. 191°. IR spectra of (III) and (IV) are identical with those reported.[3]

The neutral product of ozonolysis was consisted of two components: 1) Oil (V), $C_{10}H_{16}O_2$ (2,4-dinitrophenylhydrazone, m.p. 186°) volatile with steam. 2) Oil (VI) $C_{13}H_{22}O_2$ (monosemicarbazone, m.p. 248°) nonvolatile with steam.



V



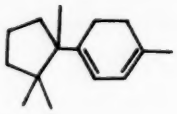
VI

---

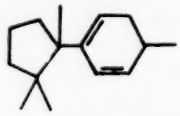
4 Molecular formula was assumed to be $C_{15}H_{24}$.

Whilst the structure of (V) was assumed to be 1,2,2-trimethylcyclopentylglyoxal from positive silver mirror test, positive Fehling test and formation of d-camphonanic acid by nitric acid oxidation, the structure of (VI) was proposed to be 1-(1',2',2'-trimethylcyclopentyl)-pentan-1,4-dione from analysis of semicarbazone, positive iodoform test and formation of d-camphonanic acid upon nitric acid oxidation. (V) and (VI) gives only monocarbonyl derivatives showing large steric hindrance on the second carbonyl group.

Since it is known that cuparene is stable[s] under ozonization condition used, one could draw a conclusion that the fraction (I) contains dihydrocuparenes, to which the authors wish to attribute the name cuprenene. There might be two cuprenenes in the fraction (I), one of which, α-cuprenene (B), afforded (VI), the other, β-cuprenene (C), giving compound (V). However,



B



C

methylsuccinic acid, which should be resulted from β-cuprenene, was failed to be detected.

The fraction (I) also contains some cuparene, presence of which could be revealed from absorption bands at 1520, 810 cm^{-1} in its IR spectrum. Cuprenenes easily undergo dehydrogenation on mild oxidation with permanganate, chromic acid or ozone or even on standing in air. The fact is shown from the disapearance of bands at 1640, 886 cm^{-1} in its IR spectrum and change in UV spectrum (from λ_{max}^{MeOH} 265 mμ (log ε 3.41) to λ_{max}^{MeOH} 218, 265 mμ (log ε 3.88, 2.53)) and separation of some water on every distillation of the fraction.

It might be appropriate to suppose that cuparene is a secondary product

and cuprenene is the real constituent of Thujopsis dolabrata.

1,2,2-trimethyl cyclopentylbromide, m.p. 43°, obtained from d-camphonanic acid by Hansdiecker reaction, was converted to lithio-compound and condensed with p-bromotoluene to give dl-cuparene. The identity was established by the comparison of IR spectra, N.M.R spectra (in $CHCl_3/CCl_4$), gas chromatography (with Reoplex 400- Celite 545, 190°C, He 50 ml/min retention time 204 sec) and by the formation of dl-cuparenic acid (S-p-Bromobenzylthiouronium salt, m.p. 182°).

Authors' thanks are due to Takasago Perfumery Co. for generous gift of material which made possible for them to perform this investigation.

1960

Tetrahedron Letters No. 23, pp. 18-21, 1960. Pergamon Press Ltd. Printed in Great Britain

THERMAL DECOMPOSITION OF 1-AZO-BIS-1-PHENYLETHANE: ACCELERATION BY CHLORANIL

Raymond C. Petersen and Sidney D. Ross

Research Laboratories, Sprague Electric Company

North Adams, Massachusetts

(Received 8 September 1960)

THE rate of the thermal decomposition of 1-azo-bis-1-phenylethane, A, has been measured in the presence of chloranil, C, and MgO in N-methylpropionamide, NMP, solvent. It was found that chloranil produced a significant increase in the rate of decomposition, while the suspension of MgO was necessary to neutralize an acid reaction product which halted the decomposition, probably through catalyzing the isomerization of the azo compound to the corresponding hydrazone.

The course of the reaction was followed by measuring nitrogen evolution as a function of time with the reaction cell in a constant temperature bath which was maintained at 97.30 ± 0.14° throughout the runs reported here.

The decomposition was found to be first order in $\underline{A}$ to a high percentage reaction and the first-order rate constants were found to be proportional to $\underline{C}_o/\sqrt{\underline{A}_o}$ where $\underline{C}$ and $\underline{A}$ are mole fractions of C and A respectively, and the subscripts refer to zero time. Table 1 presents the first-order rate constants k together with values of $\underline{A}_o$, $\underline{C}_o$ and $\underline{C}_o/\sqrt{\underline{A}_o}$. The rate constants were obtained by a least squares treatment of values of $\ln \underline{A}_o/\underline{A}$ vs. time $\underline{t}$, using data obtained between 10% and 60% reaction.

1960

TABLE I

$A_o \times 10^3$ mole fract.	$C_o \times 10^3$ mole fract.	$C_o/\sqrt{A_o} \times 10^2$	$k \times 10^5$ sec^{-1}
8.046	0	0	3.773
6.914	2.475	2.977	4.312
8.469	4.159	4.519	4.420
2.188	2.161	4.620	4.600
5.958	5.099	6.606	4.985
2.149	3.166	6.830	4.723
8.078	7.950	8.845	5.182
7.892	7.858	8.845	5.198

A least squares treatment of k vs. $C_o/\sqrt{A_o}$ gives a slope of 1.575×10^{-4} and an intercept of 3.798×10^{-5} sec^{-1} with an average deviation of 1.47%. The intercept agrees almost perfectly with first-order rate constants obtained for the decomposition of A in both NMP and diphenylmethane with nothing added as it does with the value (3.78×10^{-5} sec^{-1}) obtained by extrapolation from the data of Cohen, et al.,[1] at two slightly higher temperatures in ethylbenzene.

The data can be fitted by assuming the following reactions to be the only kinetically significant ones:

$$A \xrightarrow{k_1} N_2 + 2R\cdot \qquad (1)$$

$$R\cdot + C \xrightarrow{k_2} RC\cdot \qquad (2)$$

$$RC\cdot + A \xrightarrow{k_3} RCR + N_2 + R\cdot \qquad (3)$$

$$R\cdot + R\cdot \xrightarrow{k_4} R_2 \qquad (4)$$

where R· is the 1-phenylethyl radical and RC· symbolizes the

[1] S. G. Cohen, S. J. Groszos and D. B. Sparrow, J. Am. Chem. Soc. 72, 3947 (1950).

product(s) of attack by R· on C. There is a wide variety of possibilities for the chemical identities of RC· and RCR, essentially unlimited by kinetic restrictions. In this situation, product analyses cannot identify with any certainty the species important in step 3.

Applying the steady-state approximation to R· and RC· yields the rate equation

$$-\frac{d\underline{A}}{d\underline{t}} = \underline{A}\left[k_1 + k_2\sqrt{\frac{k_1}{k_4}}\,\frac{\underline{C}}{\sqrt{\underline{A}}}\right], \qquad (5)$$

Since individual runs are cleanly first order in $\underline{A}$, the experimental first order rate constant can be written

$$k = k_1 + k_2\sqrt{\frac{k_1}{k_4}}\,\frac{\underline{C}}{\sqrt{\underline{A}}} = k_1 + k_2\sqrt{\frac{k_1}{k_4}}\,\frac{\underline{C}_o}{\sqrt{\underline{A}_o}}. \qquad (6)$$

This is predictable since both $\underline{C}$ and $\underline{A}$ decrease as the reaction proceeds, with $\underline{C}$ decreasing less rapidly than $\underline{A}$, and under these conditions the function $\underline{C}/\sqrt{\underline{A}}$ is not very dependent on time regardless of the exact stoichiometry.

It is interesting to note that, while step 3 is most important in determining the functional dependence of rate on $\underline{C}$ and $\underline{A}$, k_3 does not appear in the final rate expression.

Applying the rate data to equation 6 gives $k_1 = 3.798 \times 10^{-5}$ sec $^{-1}$ and $k_2/\sqrt{k_4} = 2.555 \times 10^{-2}$ sec $^{-1/2}$. Rate constants are given in four figures for the least squares treatment, but the fourth figure is certainly doubtful. Also, there is evidence of side reactions with chloranil present which contribute an error to the value of $k_2/\sqrt{k_4}$.

Step 1 is kinetically indistinguishable from the sequence

$$A \rightleftharpoons [R\cdot + \cdot N{=}N{-}R] \longrightarrow N_2 + 2R\cdot \qquad (7)$$

where brackets indicate a solvent cage. The radical RC· can thus react with either A, the cage or both with no observable kinetic difference.

The nature of step 3 in the reaction scheme is of particular pertinence to the question of mechanism. It is improbable that this step represents an induced decomposition of A, since a separate study has shown that the rate of decomposition of A is increased by 1,1-diphenyl-2-picrylhydrazyl. In this case attack by the DPPH radical on A seems unlikely due to the size of the radical and to its relatively low reactivity.

A reasonable possibility involves formation of a complex between RC· and A,[2] which complex may then decompose to give N_2 at a faster rate than does A itself.

---

[2] C. E. Boozer and G. S. Hammond, J. Am. Chem. Soc. 76, 3861 (1954).

Tetrahedron Letters No. 23, pp. 22-24, 1960. Pergamon Press Ltd. Printed in Great Britain

GIBBERELLIN A_9

B.E. Cross, R.H.B. Galt and J.R. Hanson

Imperial Chemical Industries Limited,
Akers Research Laboratories, Welwyn, Herts.

(Received 16 September 1960)

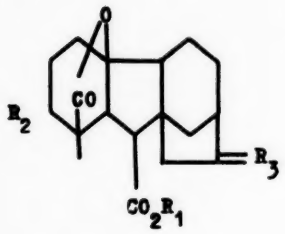
A more detailed examination of the crude acidic metabolites produced in the fermentation of Gibberella fujikuroi described in our earlier communication[1] has revealed the presence of a new acid. The gummy fraction eluted from the charcoal-celite column[1] with water containing 80% acetone has been rechromatographed on silica-celite (1:2). Elution with 10% ethyl acetate in light petroleum afforded a plant growth promoting acid for which we propose the name gibberellin A_9.

Gibberellin A_9 (I), which formed needles from acetone - light petroleum (b.p. 60-80°), m.p. 208-211° dec., $[\alpha]_D^{22}$ -12° (EtOH), ν_{max}^{Nujol} 3098 (OH of carboxyl), 1740, 1723, 1659 and 893 cm $^{-1}$, and its methyl ester (II), m.p. 136°, $[\alpha]_D^{22}$ -15° (EtOH), ν_{max}^{Nujol} 1777 (γ-lactone), 1738 (ester), 1659 and 873 ($=CH_2$) cm $^{-1}$, gave analyses consistent with the formula $C_{19}H_{24}O_4$ for the acid (I). Microhydrogenation of (II) revealed the presence of one double bond, shown to be a terminal methylene

---

[1] B.E. Cross, R.H.B. Galt and J.R. Hanson, Tetrahedron Letters No. 15, 18 (1960).

group exocyclic to a 5-membered ring by ozonolysis of (II) to formaldehyde (0.6 mol.) and a nor-ketone (III), $C_{19}H_{24}O_5$, m.p. 204-207°, ν_{max}^{Nujol} 1772 (γ-lactone), 1738 (ester and 5-ring ketone) cm^{-1}. Structure (I) for gibberellin A_9, suggested by the above results, was established by degradation of gibberellin A_4 (IV)[2,3] to (III). The tosylate (V) of gibberellin A_4 methyl ester nor-ketone (VI)[4] with boiling collidine



	R_1	R_2	R_3
I	H	H	CH_2
II	Me	H	CH_2
III	Me	H	O
IV	H	OH	CH_2
V	Me	TsO	O
VI	Me	OH	O
VII	Me	AcO	O

gave a Δ^2-olefin, $C_{19}H_{22}O_5$, m.p. 160-161°, which on catalytic hydrogenation afforded a product identical in all respects with gibberellin A_9 methyl ester nor-ketone (III).

The structures of gibberellins A_7 and A_9 are both dependent upon that of gibberellin A_4 which has been related[3] to gibberellin A_1 ——

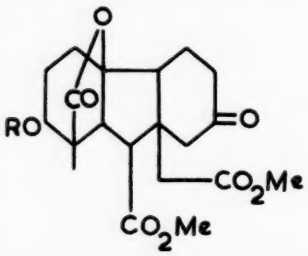
---

[2] P.W. Brian, J.F. Grove and J. MacMillan, "The Gibberellins" in Zechmeister, Prog. Chem. Org. Nat Prod. 18, 350 (1960).

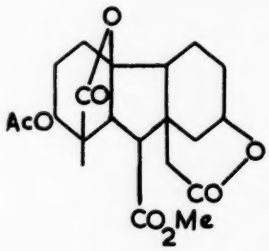
[3] H. Kitamura, N. Takahashi, Y. Seta, A. Kawarada and Y. Sumiki, Bull. Agric. Chem. Soc. Japan 23, 344 (1959).

[4] N. Takahashi, Y. Seta, H. Kitamura and Y. Sumiki, ibid. 23, 405 (1959).

and hence to gibberellic acid[5,2] —— by Sumiki and his co-workers. We have confirmed this relationship by a new series of reactions. Acetylation of the keto-ester (VIII), derived from gibberellic acid,[6] yielded the acetate (IX), m.p. 193-195°, which on hydrogenation (Adams



(VIII) R=H
(IX) R=Ac



(X)

catalyst) in acetic acid containing a trace of perchloric acid afforded the δ-lactone (X), m.p. 193-194°, $\nu_{max}^{CHBr_3}$ 1774 and 1738 (broad) cm $^{-1}$. Baeyer-Villiger oxidation of the acetate of gibberellin A_4 methyl ester nor-ketone (VII), m.p. 189°, $\nu_{max}^{CHBr_3}$ 1771, 1738 cm $^{-1}$, with perbenzoic acid gave the same δ-lactone (X).

All structures are supported by satisfactory analyses.

---

[5] J.F. Grove, P.W. Jeffs and T.P.C. Mulholland, J. Chem. Soc. 1236 (1958).

[6] B.E. Cross, J. Chem. Soc. 3022 (1960).

Tetrahedron Letters No. 23, pp. 25-29, 1960. Pergamon Press Ltd. Printed in Great Britain

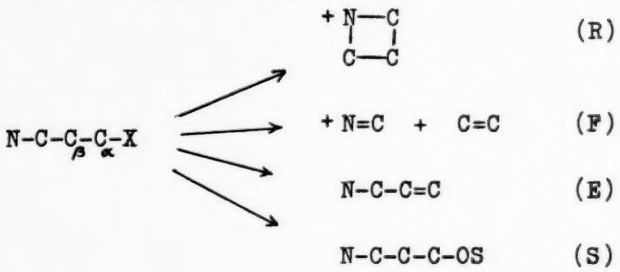
MECHANISTISCHE UEBERGAENGE BEI DER SOLVOLYSE VON γ-AMINOPROPYLCHLORIDEN

C.A. Grob und F.A. Jenny

Organisch-chemisches Institut der Universität Basel.

(Received 29 September 1960)

Bei der Solvolyse von γ-Aminohalogeniden ist mit mindestens vier Reaktionen zu rechnen, nämlich Ringschluss (R) zu einem Azetidiniumsalz, Fragmentierung (F) zu einem Carbiminiumsalz und einem Olefin, 1,2-Eliminierung (E) zu einem Aminoolefin und Substitution (S) durch das Lösungsmittel[1,2]:



Das Hervortreten jeder dieser Reaktionen ist durch das Ausmass der Alkylsubstitution in α- und β-Stellung bedingt, wie die vergleichende Untersuchung der sechs γ-Aminohalogenide (1) bis (6) der Tabelle zeigt.

---

[1] C.A. Grob, "Theoretical Organic Chemistry;" Report on the Kekulé Symposium, London 1958, S. 114.

[2] C.A. Grob, Bull. Soc. Chim. Fr. 1360 (1960).

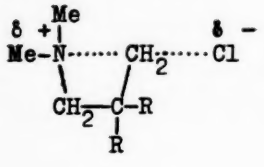
		$k_1 \cdot 10^5$	k_{rel}	k_1/k_{RCl}	Produkte[a] %
(1)	$Me_2NCH_2CH_2CH_2Cl$	10,8	5,8	ca. 6.10^3	100 R
(2)	$Me_2NCH_2\overset{Me}{\underset{Me}{C}}-CH_2Cl$	98	52,5	ca. 5.10^6	100 R
(3)	$Me_2NCH_2CH_2\overset{Me}{C}H-Cl$	1,87	1	225	100 R
(4)	$Me_2NCH_2\overset{MeMe}{\underset{Me}{C}}-CH-Cl$	28,2	15	3400	72 R, 19 F
(5)	$Me_2NCH_2CH_2\overset{Me}{\underset{Me}{C}}-Cl$	35,5	19	0,75	44 F, 38 S, 9 E
(6)	$Me_2NCH_2\overset{MeMe}{\underset{MeMe}{C}}-C-Cl$	14500[b]	7750	125[c]	72 F, 20 E

[a] bei der Reaktion in Wasser; [b] extrapoliert; [c] bei 25° verglichen.

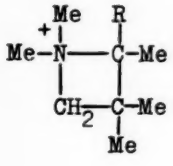
1960

Von diesen Paaren primärer, sekundärer und tertiärer γ-Aminopropylchloride ist jeweils eines am β-Kohlenstoffatom unsubstituiert, das andere dimethyliert. Die Reaktionsgeschwindigkeitskonstanten erster Ordnung k_1 (Kolonne 2) der Solvolyse in 80-proz. Aethanol bei 56°, sowie die relativen k_1-Werte bezogen auf Verbindung (3) (Kolonne 3) zeigen, dass die übliche Reihenfolge der solvolytischen Reaktivität (tert > sek > prim) nicht zutrifft. Mit Ausnahme des tert. Chlorids (5)[3] reagieren zudem alle Verbindungen erheblich schneller als die entsprechend gebauten Alkylchloride (RCl) ohne Aminogruppe, wie aus den Quotienten k_1/k_{RCl} (Kolonne 4) hervorgeht. Die Beschleunigung weist auf eine Unterstützung der Ionisierung des Chloratoms durch die Aminogruppe hin und ist bei den primären Chloriden (1) und (2) am meisten, bei den tertiären Chloriden (5) und (6) am wenigsten ausgeprägt.

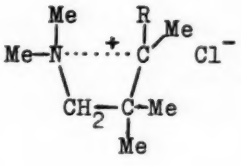
Im Falle der primären Aminochloride (1) und (2) weisen die hohen Werte der Quotienten k_1/k_{RCl} sowie die alleinige Bildung des entsprechenden Ringschlussproduktes (Kolonne 5) auf eine interne nukleophile Substitution mit dem Uebergangszustand I hin. Dieser Mechanismus dürfte auch für das sek. Chlorid (3), welches ebenfalls quantitativ ringschliesst, zutreffen.



I



II



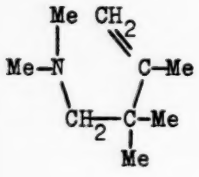
III

---

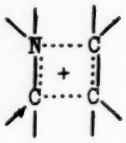
[3] Vergl. Dissertation F. Ostermayer, Basel 1958.

Obwohl die Chloride (4) und (6) 3400 bzw. 125 mal schneller reagieren als die entsprechenden Alkylchloride (Me_2CH- statt Me_2N-) und die zugehörigen Azetidiniumsalze II, R = H bzw. Me, unter den Reaktionsbedingungen stabil sind, wird beim sek. Chlorid (4) nur noch 72 %, beim tert. Chlorid (6) überhaupt kein Ringschlussprodukt mehr gefunden. Dafür treten Fragmentierungs- und Eliminierungsprodukte in Erscheinung. Die Ionisierung des Chloratoms in (4) und (6) wird also durch die Aminogruppe unterstützt, ohne dass es zum Ringschluss, d.h. zur kovalenten Bindung des Stickstoffatoms am α-Kohlenstoffatom kommt.

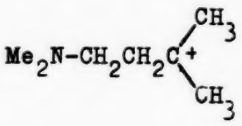
Diese Resultate können gedeutet werden, wenn ein durch das Elektronenpaar der Aminogruppe intern solvatisiertes Carboniumion III als Zwischenprodukt angenommen wird. Dieses kann anschliessend Ringschluss, Fragmentierung oder 1,2-Eliminierung erleiden. So führt stärkere Koordinierung des α-Kohlenstoffatoms durch die Aminogruppe im Falle des sek. Carboniumiones III, R = H, aus (4) zum extern solvatisierten Ringschlussprodukt II, R = H. Bei dem gegen nukleophilen Angriff am α-Kohlenstoffatom mehr gehinderten Kation III, R = Me, aus (6), tritt auch Bildung des Aminoolefins IV unter Verlust eines Protons als Folgereaktion auf.



IV



V



VI

Im kationischen Zwischenprodukt sowohl aus (4) als auch aus (6) führt die Dehnung der C_β-C_γ-Bindung zum Uebergangszustand V der Fragmentierung. Das Fehlen von Substitutionsprodukten bei der Hydrolyse von (4) und (6) spricht dafür, dass auch die Vorderseite des intern solvatisierten Carboniumiones III gegen Angriff des Lösungsmittels abgeschirmt ist, was durch die Ionenpaar-Formulierung III zum Ausdruck kommt.

Das tert. Chlorid (5) ionisiert, wie schon früher gezeigt worden ist[1,3], ohne Unterstützung durch die Aminogruppe zum gewöhnlichen Carboniumion VI, welches anschliessend in Fragmentierungs-, Substitutions- und Eliminierungsprodukte übergeht.

Sowohl bei den primären als auch bei den sekundären und tertiären Chloriden wird die Beteiligung der Aminogruppe am Ionisierungsprozess durch die geminalen Methylgruppen am β-Kohlenstoffatom erhöht. Diese Wirkung kann zustande kommen, indem die Methylgruppen die Häufigkeit von quasi-Ringkonstellationen, wie in I und III, fördern, und indem sie den Valenzwinkel $C_\alpha C_\beta C_\gamma$ gegenüber einer Methylengruppe verkleinern.

Die drei erwähnten Mechanismen der Solvolyse von γ-Aminohalogeniden unterscheiden sich durch den Grad der Beteiligung des γ-Aminostickstoffatoms im Uebergangszustand. Im Falle von (1), (2) und (3) hat die Beteiligung nukleophilen Charakter. Bei (4) und (6) ist diese im wesentlichen elektrostatisch durch den atomaren Dipol des freien Elektronenpaares bedingt. Bei (5) ist die Aminogruppe überhaupt nicht mehr direkt an der Ionisierung beteiligt. Auffällig ist, dass der synchrone Fragmentierungsmechanismus, der bei starren γ-Aminohalogeniden mit geeigneter Stereochemie vorherrscht[2], beim vorliegenden Typus nicht auftritt.

---

[3] Vergl. Dissertation F. Ostermayer, Basel 1958.

Tetrahedron Letters No. 23, pp. 30-34, 1960. Pergamon Press Ltd. Printed in Great Britain

REACTION SELECTIVITY, HYDROGEN ISOTOPE EFFECT AND STERIC HINDRANCE IN THE AROMATIC HALOGENATION OF POLYALKYLBENZENES[1]

Enrico Baciocchi, Gabriello Illuminati and Giancarlo Sleiter

Department of Chemistry, University of Trieste

Trieste, Italy

(Received 11 October 1960)

The observation that aromatic halogenation with molecular halogen is a less selective reaction with polymethylbenzenes than with monosubstituted benzenes, as based on the reaction constants of the reactions in each individual series[2,3], suggests that the two methyl groups ortho to the attacked position in the former molecules may effectively lower the sensitivity of the reagent to the changes of the electron density of the aromatic substrate by hindering the approach of the attacking entity. Presumably a steric effect of this kind may alter the detailed timing of the process and be accompanied by a shift of the reaction coordinate for the rate-determining transition state toward increasing extents of C-H bond breaking, in the potential energy curve of the reaction. If bond breaking made enough progress, a hydrogen isotope effect would result in the aromatic halogenation of hindered polymethylbenzenes.

---

[1] Substitution in Polymethylbenzenes. XII.

[2] H.C.Brown and Y.Okamoto, J.Am.Chem.Soc. 80, 4979 (1958).

[3] (a) G.Illuminati, J.Am.Chem.Soc. 80, 4941 (1958); (b) E.Baciocchi and G.Illuminati, Ric.Sci. 28, 1159 (1958).

The possible connection of the specific steric environment characteristic of these systems to the selectivity of the reaction and to hydrogen isotope effects is being tested in this Laboratory by extension of our studies to more hindered polyalkylbenzenes. The results concerning isotope effects in the case of one of the polyalkylbenzene structures involving two ortho methyl groups flanking the attacked position (bromodurene) have been obtained recently in this Laboratory and the very recent report of a hydrogen isotope effect in the bromination of T-labeled 1,3,5-tri-t-butylbenzene[4] prompts us to communicate our present halogenation data with 3-bromo-6-deutero-durene and 3-bromodurene.

Consistent syntheses of the two compounds were effected starting from the same stock of 3,6-dibromodurene and letting it to react with n-butyl lithium in ether solution 0.06 M in each reactant and under standard conditions for the synthesis of deuterated compounds[5]. 3-Bromoduryl lithium, which was formed quantitatively by halogen-metal interconversion within twelve minutes at room temperature, was then hydrolyzed with 96% heavy water or water to give 3-bromo-6-deuterodurene and 3-bromodurene, respectively. The consistency in the synthesis of the two compounds insured the validity of the comparison of the subsequent rate measurements. The latter were carried out according to the procedure described previously for the study of bromination with Br_2

---

[4] P.C.Myhre, Acta Chem.Scand. 14, 219 (1960).

[5] See, for example, L.H.P.Weldon and C.L.Wilson, J.Chem.Soc.235 (1946).

in nitromethane[6] and chlorination with Cl_2 in glacial acetic acid[3b]. The results are collected in Table 1.

TABLE 1

Halogenation Data at 30°C for the Hydrogen Isotope Effect in Bromodurene

Aromatic compound	Bromination in $MeNO_2$		Chlorination in AcOH	
	t_{10}(mins.)(a)	k_H/k_D	k, $l \times mole^{-1} \times sec^{-1}$	k_H/k_D
3-Bromodurene	22.9±1.2	1.4	0.098	~1
3-Bromo-6-deutero-durene	32.7±1.8		0.107	

(a) Times for 10% reaction with solutions 0.01 M in each reactant. Data obtained with a single stock of nitromethane, for which relative rates of bromination were ascertained to be identical to those reported previously[3a,6].

The k_H/k_D ratios were calculated by neglecting any nuclear hydrogen content in the deuterium compound and infrared analysis in fact indicated such a content to be low. Thus, Table 1 shows that there

---

[6] G.Illuminati and G.Marino, J.Am.Chem.Soc. 78, 4975 (1956).

is a definite, even though small, isotope effect in the bromination of bromodurene and that, presumably, the corresponding k_H/k_D value, 1.4, is a lower experimental limit. In contrast to this, chlorination of the same system shows no isotope effect.

Since the demonstration that isotope effects are absent in the bromination of such simple aromatic hydrocarbons as benzene[7,8], a number of recent papers reports varying extents of such effects in the halogenation of more perturbed or more complex aromatic molecules. Thus, small to fairly large effects have been found in the halogenation of anisole[9], aniline[10] and dimethylaniline[10,11], i.e., of systems containing strong electron-releasing substituents and a large effect in the bromination of the highly hindered 1,3,5-tri-t-butylbenzene[4]. Clearly, from the published data isotope effects depend not only on the isotope used (T > D) but also on the type of the halogenation reaction (iodination > bromination > chlorination) and on the structure of the aromatic substrate. In the case of the bromination of monosubstituted benzenes with molecular bromine, an isotope effect has been clearly established with the dimethylamino group[11] but not with the less strongly electron-releasing methoxy group[9]. Our present

---

7 L.Melander, Arkiv f.Kemi 2, 211 (1950).

8 P.B.D.De La Mare, T.M.Dunn and J.T.Harvey, J.Chem.Soc. 923 (1957).

9 E.Berliner, Chem.& Ind. 177 (1960)

10 E.Shilov and F.Weinstein, Nature 182, 1300 (1958)

11 P.G.Farrell and S.F.Mason, Nature 183, 250 (1959)

results with bromodurene now offer another case of a hydrogen isotope effect for the bromination reaction with molecular bromine. Bromodurene does not contain any strong electron-releasing group, but the seat of the reaction is hindered by two ortho methyl groups : it is then probable that the small effect found belongs to the same class of that shown by 1,3,5-tri-t-butylbenzene. The over-all activation does not seem to be alone a determining factor[10] and, in any case, on the base of the additivity of the electronic effects in polysubstituted aromatic compounds, the only available nuclear position of bromodurene is less activated than the para-position of anisole, for which no more than an effect within experimental uncertainty was found[9]. The influence of steric hindrance on hydrogen isotope effects was well established by Zollinger for the diazo-coupling of naphthalene systems; however, the announced isotope effect in the bromination of 2-naphthol-6,8-disulphonic acid[12] might result from a combination of steric and electronic effects because of the presence of the OH substituent.

From the above, it should be clear that further experimentation is needed to neatly distinguish among all possible correlations of isotope effects with the nature of the reagent and the structure of the substrate in aromatic halogenation. Extension of the present work to other molecules in the polyalkylbenzene area will be reported in due course.

The authors are grateful to the Italian Research Council (C.N.R.) for financial support which made this work possible.

---

[12] Hch.Zollinger, Experientia 12, 165 (1956).

Tetrahedron Letters No. 23, pp. 35-37, 1960. Pergamon Press Ltd.
Printed in Great Britain

1960

THE MOLECULAR STRUCTURE AND ABSOLUTE CONFIGURATION OF JACOBINE BROMHYDRIN

J. Fridrichsons, A. McL. Mathieson

Division of Chemical Physics, C.S.I.R.O. Chemical Research Laboratories, Melbourne, Australia

and D. J. Sutor*

Organic Chemistry Section, C.S.I.R.O. Chemical Research Laboratories, Melbourne, Australia

(Received 10 October 1960)

THE bromhydrin of jacobine, $C_{18}H_{26}NO_6Br$, crystallises from ethanol in space group $P2_1$ with cell dimensions, $\underline{a} = 9.88_9$, $\underline{b} = 15.3$, $c = 14.63_4$Å, $\beta = 112.7°$ at -150°C. Unit cell contents are $2(2 \times C_{18}H_{26}NO_6Br + C_2H_5OH)$. X-ray analysis based on 0-10 layers about the $\underline{b}$ axis (3327 reflections of 3496 theoretically possible) has yielded the three-dimensional arrangement of the 55 atoms constituting the skeletons of the two jacobine bromhydrin molecules and the ethanol molecule[1]. The two molecules of jacobine bromhydrin which are crystallographically independent are identical to the first order, thus providing additional internal evidence of the essential correctness of the molecular structure. When the molecular structure had been determined, the absolute configuration was defined by application of Bijvoet's[2] technique using the anomalous dispersion of the bromine atoms.

---

*Present address: Birkbeck College, University of London, London WC1, U.K.

[1]A. McL. Mathieson, I.U.P.A.C. Symposium on the Chemistry of Natural Products, Australia (1960) (to be published by Butterworths Scientific Publications, London).

[2]J. M. Bijvoet, A. F. Peerdeman and A. J. van Bommel, Nature 168, 271 (1951).

The three-dimensional atomic distribution of the jacobine bromhydrin molecule, as viewed down the b axis, is given in the correct absolute orientation in Fig. 1a while a more conventional chemical formulation is presented in Fig. 1b.

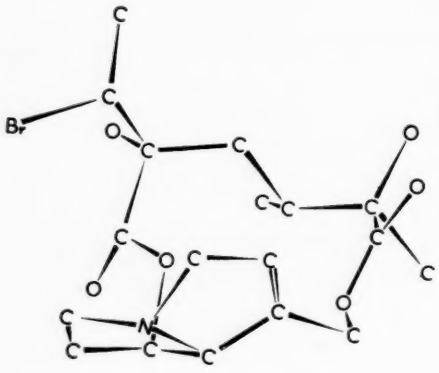


Fig. 1a.

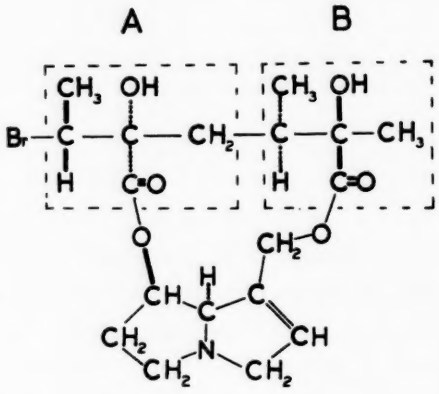


Fig. 1b.

The structure is in agreement with the reformulation of jacobine proposed by Geissman[3] on the basis of re-assessment of the available chemical and spectral evidence (see also Bradbury and Masamune[4]). Additional support for Geissman's reformulation of jacobine is also available in the X-ray analysis of its bromdilactone, $C_{10}H_{13}O_4Br$, which will be reported independently by Taylor[5].

---

[3] T. A. Geissman, Austral. J. Chem. 12, 247 (1959).

[4] R. B. Bradbury and S. Masamune, J. Amer. Chem. Soc. 81, 5201 (1959).

[5] J. C. Taylor, International Symposium on the Chemistry of Natural Products, Abstracts p.43 (1960).

The analysis of jacobine bromhydrin provides independent proof of the absolute configuration of the retronecine component[6] and defines, for the first time, both the relative internal and the absolute configuration of the jaconecic acid component.

The method of structure analysis and details of the stereochemistry of the molecule will be presented later, but one aspect of the stereochemistry is worthy of note here. Inspection of the three-dimensional atom model of the crystal structure revealed that the jaconecic acid component is composed of two parts whose carbon and oxygen skeletons are identical in their spatial arrangement but antipodal in configuration. The two parts are within the dotted boxes, A and B in Fig. 1b. Their spatial arrangement can also be deduced from inspection of Fig. 1a.

It is tempting to suggest that the two units A and B are derived from an isoprenoid precursor e.g. angelic acid. It would appear possible that detailed configuration evidence of this type may provide an additional guide in the elucidation of the biogenetic origin of the Senecio alkaloids.

---

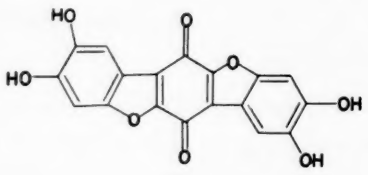
[6] N. J. Leonard, The Alkaloids Vol. VI, Chap. 3. Senecio Alkaloids Academic Press (1960).

Tetrahedron Letters No. 23, pp. 38-39, 1960. Pergamon Press Ltd. Printed in Great Britain

ERRATA

1. K. AGHORAMURTHY, K. G. SARMA and T. R. SESHADRI: The structure of thelephoric acid, Tetrahedron Letters No. 16, 4-10 (1960).

The authors regret that an incorrect formula III was submitted and published in the above article. The correct formula reads as follows:



III

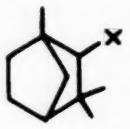
2. JEROME A. BERSON: Apportionments of products from unsymmetrically substituted carbonium ions, Tetrahedron Letters No. 16, 17-20 (1960).

The author regrets the following errors which appeared in the above article.

(a) p. 18, line 17: for "pinyl-fenchyl (VIII-IIIB)" read "pinyl-fenchyl (VIIIA-X)";

(b) p. 18, line 11: for VIIIA-IIIB" read "VIIIA-X";

(c) the formula marked VIIIA on p. 18 should read:



X

Dr. Berson has also requested the publication of the following Addendum.

J. D. Roberts (Abstracts of Papers, Sixtenth National Organic Chemistry Symposium of the American Chemical Society, Seattle, Washington, June 1959) accounted for the distribution of products from the 1-methylcyclobutyl-1-methylcyclopropyl carbinyl-methylallylcarbinyl carbonium ion system in terms similar to those I outlined for the bicyclic and acyclic cases.

3. J. F. BIELLMANN, D. FRACETIC et G. OURISSON: Effets conformationnels sur l'équilibre cis-trans d'α-hydrindanones, Tetrahedron Letters No. 18, 4-9 (1960).

The authors regret the following errors which appeared in the above article.

(a) p. 4 ligne 3 avant la fin : au lieu de "(V)", lire "(IV')"

(b) p. 5 Tableau 1, Formule V : au lieu de "(V)", lire "(IV')"
dernière ligne de constantes: lire "IV':F=142°"

(c) p. 5 Tableau 2, Colonne de droite; cadre du haut: ajouter IV
cadre du bas : ajouter IX

Tetrahedron Letters No. 24, pp. 1-6, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

AN INTERPRETATION OF THE KINETICS OF BIMOLECULAR SUBSTITUTION BY ANIONIC BASES IN ALCOHOL-WATER MIXTURES

R. G. Burns and B. D. England

Chemistry Department, Victoria University of Wellington,

Wellington, New Zealand

(Received 8 October 1960)

IT has been difficult for many years to understand the large difference in behaviour of bimolecular nucleophilic substitution reactions between basic anions and organic halides in methanol-water mixtures and ethanol-water mixtures. If reactions of this type are studied initially in dry methanol and dry ethanol, and if water is then added to each of these solvents, the rate constant for alkaline hydrolysis falls in the case of ethanol-water mixtures, but, with methanol-water mixtures, rises initially, passes through a maximum, and then falls as still more water is added. This behaviour was observed by de Bruyn and Steger[1] for the alkaline hydrolysis of methyl and ethyl iodides and further examples are quoted by Bunnett and Zahler[2] for aromatic nucleophilic substitution reactions.

The fall observed with ethanol-water mixtures in the case of aliphatic halides (S_N2 reactions) is apparently in accordance with the behaviour

---

[1] C.A.L. de Bruyn and A. Steger, Rec. Trav. Chim. 18, 311 (1899); Z. Phys. Chem. 49, 336 (1904).

[2] J. Bunnett and R.E. Zahler, Chem. Rev. 49, 349 (1951).

expected on the basis of the Hughes-Ingold theory of solvent action,[3a] and the results of de Bruyn and Steger in ethanol-water mixtures have often[3a,4] been quoted as evidence supporting the theory. The initial rise in methanol-water mixtures is not expected and it would therefore appear that the methanol-water results are exceptional. The purpose of this communication is to introduce a different point of view, namely that it is the ethanol-water results which are atypical and to provide a reason for their lack of conformity.

In Table 1, results for various halides are collected and it is noteworthy that there is an initial rate increase in all cases in methanol-water mixtures. We have not observed any exception to this behaviour in these mixtures. The rate also rises initially in ethanol-water mixtures when sodium thiophenoxide is the added reagent and there is also some evidence[5] for an initial rise with sodium acetate and ethyl iodide in this medium.

In Fig. 1, results of various workers for the base composition in alkaline alcohol-water mixtures are given. These include results obtained in this department by kinetic methods similar in principle to those previously used in phenol-methanol mixtures.[6] Other workers have used thermodynamic methods. Although the curves should be regarded as approximate,

---

[3] C.K. Ingold, Structure and Mechanism in Organic Chemistry [a] p. 348; [b] p. 349; [c] p. 460. Cornell University Press, Ithaca (1953).

[4a] A.E. Remick, Electronic Interpretations of Organic Chemistry p. 283. John Wiley, New York (1949); [b] K.J. Laidler, Chemical Kinetics p. 131. McGraw-Hill, New York (1950).

[5] S. Eagle and J.C. Warner, J. Amer. Chem. Soc. 61, 488 (1939).

[6] B.D. England, Chem. & Ind. 1145 (1954).

TABLE 1

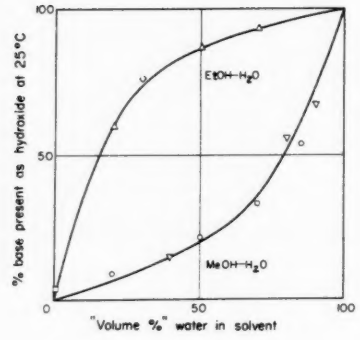
Influence of Added Water on the Overall Rate Constant for Bimolecular Nucleophilic Substitution by One or More Nucleophilic Reagents in Methanol and Ethanol. k_2 is in units of litre $mole^{-1}$ sec^{-1}.

Organic halide	Nucleophilic reagent	Rate constant	"Volume %" water in solvent				
			0	10	20	30	40
			Ethanol-water mixtures				
CH_3I	$OEt^- + OH^-$	$k_2^{25} \times 10^3$	1.62	1.26	0.89	0.64	0.50
CH_3I	$C_6H_5S^-$ [c]	$k_2^0 \times 10$	4.04	4.86	5.21	5.16	4.35
C_2H_5I [a]	$OEt^- + OH^-$	$k_2^{25} \times 10^4$	2.80	2.50	2.00	1.75	1.43
24DNCB [b]	$OEt^- + OH^-$	$k_2^{25} \times 10^2$	8.20	5.67	4.30	3.19	-
24DNCB	$C_6H_5S^-$	$k_2^0 \times 10^{-1}$	2.84	3.73	4.14	4.31	-
			Methanol-water mixtures				
CH_3I	$OMe^- + OH^-$	$k_2^{25} \times 10^4$	2.56	3.03	3.40	3.47	-
CH_3I	$C_6H_5S^-$	$k_2^0 \times 10$	1.10	1.29	1.62	1.96	2.20
C_2H_5I [a]	$OMe^- + OH^-$	$k_2^{25} \times 10^5$	8.75	11.3	13.1	16.0	16.0
24DNCB	$OMe^- + OH^-$	$k_2^{25} \times 10^2$	2.60	2.88	3.14	-	-
24DNCB	$C_6H_5S^-$	k_2^0	3.68	5.06	6.38	7.82	8.36

[a] Data from ref. 1. The constants here are probably in error by a nearly constant factor; we found this with the results of these authors for methyl iodide. All other measurements by present authors.

[b] 1-Chloro-2:4-dinitrobenzene.

[c] Thiophenoxide is probably converted in part to ethoxide, to methoxide and to hydroxide (in the more aqueous solvents).



O Quoted by Bender and Glasson[7] from the results of Koskikallio[8]

Δ Quoted by Bender and Glasson[7] from the results of Caldin and Long[8]

□ Caldin and Long[9]

▽ Alet[10]

◇ Present work

FIG. 1.

it is apparent that there is a surprisingly large proportion of hydroxide in alkaline ethanol-water mixtures containing only a small percentage of water; the corresponding proportion in methanol-water mixtures is very much less.

The mixture of anionic bases arises from the equilibrium $ROH + OH^- \rightleftharpoons H_2O + OR^-$. Although the existence of these equilibria has been recognised by many authors, others[3b,3c,11] appear sometimes to have ignored the existence of a second nucleophilic anion in alkaline ethanol-water mixtures. It now seems that the dominating factor causing the

---

[7] M.L. Bender and W.A. Glasson, J. Amer. Chem. Soc. 81, 1590 (1959).

[8] J. Koskikallio, Suomen Kemistilehti 30B, 111 (1957).

[9] E.F. Caldin and G. Long, J. Chem. Soc. 3737 (1954).

[10] (Miss) I.R. Alet, M. Sc. Thesis, Wellington, N.Z. (1958).

[11] G.H. Grant and C.N. Hinshelwood, J. Chem. Soc. 258 (1933).

decrease in the overall rate of substitution in these mixtures, as water is added initially, is the progressive change of nucleophilic reagent from ethoxide to hydroxide. Previously[3a,4] the decrease in rate in S_N2 reactions has been attributed to the effect of the changing solvent on the solvation of initial and transition states, thereby increasing the activation energy of the reaction of the halide with a single nucleophile, and it would seem that this factor plays only a minor role in alkaline methanol- and ethanol-water mixtures near the 100% alcohol region.

Sodium thiophenoxide should be less susceptible to conversion into hydroxide as water is added for, although it is a strong nucleophilic reagent, it is relatively weak as a base.[12]

With alkaline methanol-water mixtures and with thiophenoxide in both methanol- and ethanol-water mixtures, what is apparently being observed in the initial stages of adding water is an influence of the changing solvent on the rate of reaction of the halide with a single nucleophilic reagent - this term being intended to include both a fully formed anion and loose complexes of the same ion with cations or with the solvent. There is evidence[13] for the existence of such complexes and for the importance of ion pairing in determining reaction rates in various media. At the moment it is plausible to attribute the increase in rate to the progressive dissociation of alkoxide, thiophenoxide and possible hydroxide ion pair complexes with cations as the solvent is made more aqueous.

---

[12] P.B.D. de la Mare and C.A. Vernon, J. Chem. Soc. 41 (1956).

[13] J.D. Reinheimer, W.F. Kieffer, S.W. Frey, J.C. Cochran and E.W. Barr, J. Amer. Chem. Soc. 80, 164 (1958); S. Winstein, L.G. Savedoff, S. Smith, I.D.R. Stevens and J.S. Gall, Tetrahedron Letters No. 9, 24 (1960).

Fig. 1 also lends credence to the view that the fall in rate which is eventually observed after the initial rise is again due to change of nucleophile to hydroxide. Such a change should result in a decrease in the overall rate for, although unambiguous data on the relative nucleophilicity of hydroxide and alkoxides is scanty, the relatively low reactivity of hydroxide has been stressed by Bunnett and Davis[14] and Bender and Glasson[7] and Alet[10] have found that it is less than that of methoxide and ethoxide when measurements are made in the same solvent.

That rate constants representing the simultaneous attack of two nucleophiles on a single halide do not drift during a run is not surprising in view of a treatment given previously.[6] The nucleophiles are in equilibrium throughout and the ratio of hydroxide and alkoxide concentrations remains virtually constant during a run despite the fact that they are being used up at different rates by the substitution processes. Moreover[6] the isolation of a large yield of alkyl ether does not necessarily mean that the constant obtained is largely characteristic of alkoxide.

Alkaline ethanol-water mixtures have been a popular medium for the investigation of substitution reactions, elimination reactions and mixtures of these types, as well as for mechanistic studies of more complex reactions. It is evident that a considerable re-interpretation of the results that have been obtained is now necessary.

We acknowledge the benefit of correspondence with Professor E.D. Hughes.

---

[14] J.F. Bunnett and G.T. Davis, J. Amer. Chem. Soc. 76, 3011 (1954); Ibid. 80, 4337 (1958).

Tetrahedron Letters No. 24, pp. 7-12, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

STRUCTURE OF GENTIOPICROSIDE

L. Canonica, F. Pelizzoni, P. Manitto and G. Jommi

Istituto di Chimica Industriale della Università

Milano

(Received 13 October 1960)

VARIOUS structures, none of them completely satisfactory, have been proposed for the gentiopicroside (I) (Korte,[1] Sakurai[2] and Canonica[3]). Continuing our research on this subject, we have now collected a number of new experimental facts, and we wish to propose a new formula, which accounts for all the chemical and physical evidence obtained by us as well as by other authors.

The hexahydroprotogentiogenin (II) contains four oxygen atoms. In all the previous formulations, two of these were assigned to a γ-lactone system; I.R. spectra show instead the presence of a saturated δ-lactone in (II) (1746 cm^{-1} in Nujol; 1730 cm^{-1} in KBr) and of a α-β-unsaturated δ-lactone in the tetraacetylgentiopicroside (IX) and in the two isomeric tetrahydro-derivatives (VII, VIII) (1725, 1704, 1706 cm^{-1} in $CHCl_3$). This discrepancy between the proposed formulae and the spectroscopic evidence has been already

---

[1] F. Korte, Chem. Ber. 87, 512 (1954).

[2] F. Korte, Chem. Ber. 87, 780 (1954).

[3] L. Canonica and F. Pelizzoni, Gazz. Chim. Ital. 87, 1251 (1957).

indicated by Korte.[4]

The two remaining oxygen atoms of (II) must be assigned to a 2-hydroxy-tetrahydropirane system on the following evidence. (II) has reducing properties and by chromic oxidation gives a compound $C_{10}H_{14}O_4$ (III),[5,6] which is a di-δ-lactone as shown by titration and by I.R. spectrum (only one band at 1730 cm^{-1} in Nujol), and does not contain hydroxyls, ketonic groups, double bonds or active hydrogens.

Treatment with methanol in the presence of H^+ (II) gives a methylether (IV),[2] identical with that obtained from tetraacetylhexahydrogentiopicroside (V) under the same experimental conditions. The hydrolysis of (V) to give (II), and its trans-etherification to (IV), are accompanied by invertion of the configuration of the hemiacetalic carbon, as shown by the change of the molar rotatory power (ΔM = -690;-719). The entity of this change is in agreement with the values observed in other cases[7] when passing from a β-2-hydroxytetrahydropirane to a α-2-hydroxytetrahydropirane. Elimination of water, either by treatment with TsCl in Py or by heating, (II) gives a compound $C_{10}H_{14}O_3$ (VI).[8] This contains an unconjugated carbonyl as part of a lactone system (I.R. : 1725 cm^{-1}; U.V. : nil), does not contain hydroxyls, as shown by the fact the 3330 cm^{-1} band present in (II) is missing here, but contains instead a double bond of type : -O-C=C-(I.R. : 1660 cm^{-1}). Treatment with methanol in the presence of acids, (VI) gives

---

4 F. Korte, Fortschritte der Chemie Organischer Naturstoffe Vol. 17, p. 132. Wien (1959).

5 Y. Asahina, J. Asano, Y. Tanase and Y. Ueno, Chem. Ber. 69, 771 (1936).

6 F. Korte, Chem. Ber. 87, 769 (1954).

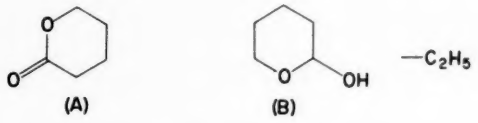
7 O. Halpern and H. Schmid, Helv. Chim. Acta 41, 1109 (1958).

8 Y. Sakurai and K. Yoshino, J.Pharm.Soc.Japan 71, 795(1951); Chem. Abstr. 46, 2499 (1952).

(IV).

(II) also contains a side-chain. This is shown to be an ethyl group because the C-methyl determination according to Kuhn Roth[9] yields propionic acid, which can be separated by V.P.C. The same result is obtained from (VII) and (VIII).

(IX) contains instead a vinyl group and gives formaldehyde on ozonolysis.[5] Therefore (II) contains: a six-membered lactone ring (A), a pirane ring (B) and a side-chain $-C_2H_5$.

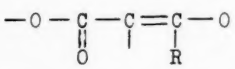


(A) (B)

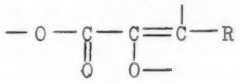
The two rings (A) and (B) must share two carbon atoms.

The U.V. spectrum of (VII) has a maximum at 247 mμ (log ε = 3.98). The only possible interpretation of this absorption, is compared with the spectra of α-β-unsaturated lactones and esters,[10] is that an etheral oxygen must be attached to the double bond conjugated with the lactone system. The chromofore in (VII) would then have one of the two structures (C) and (D):

(C)



(D)



where the etheral oxygen is that of the piranic ring and not that of the 2-hydroxyl group, as indicated by the properties of (VI).

Of the two alternative structures (C) and (D), the latter is excluded

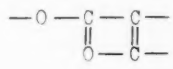
---

9 C.F. Garbers, H. Schmid and P. Karrer, Helv. Chim. Acta 37, 1336 (1954).

10 F.E. Bader, Helv. Chim. Acta 36, 215 (1953); F. Korte, J. Falbe and A. Zschocke, Tetrahedron 6, 201 (1959).

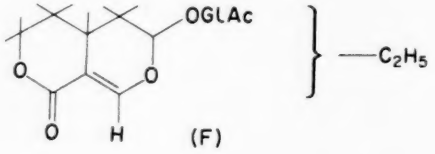
by the fact that the compound (VIII), which is formed together (VII) in the hydrogenation of (IX) and on further hydrogenation gives the same hexahydroderivate (V), still contains one conjugated double bond (λ_{max} = 230 mμ ; log ε = 3.90). This can only be part of a chromophore (E), incompatible with (D).

(E)



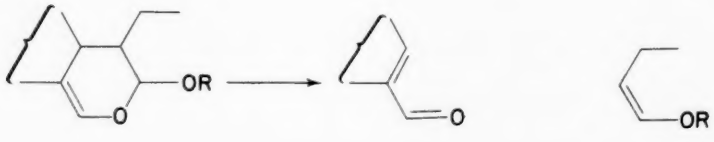
Finally, obtaining formic acid by mild hydrolysis of (X)[8] shows that in the cromophore (C) the substituent R is a hydrogen atom.

These results agree in pointing out for (VII) the partial structure (F):



(F)

The ethyl group is quite probably linked to the 3-position. In fact the pyrolysis of (XI) gives with good yields butyrric aldehyde,[5] which can be assumed to be formed by the breaking up of the pirane ring, through a retro-Diels - Alder.



On the basis of the above consideration, we propose for (I), (VII), (VIII), (II) and correlated compounds the structures of Fig. 1.

These formulations and in particular the method of linking rings (A)

1960

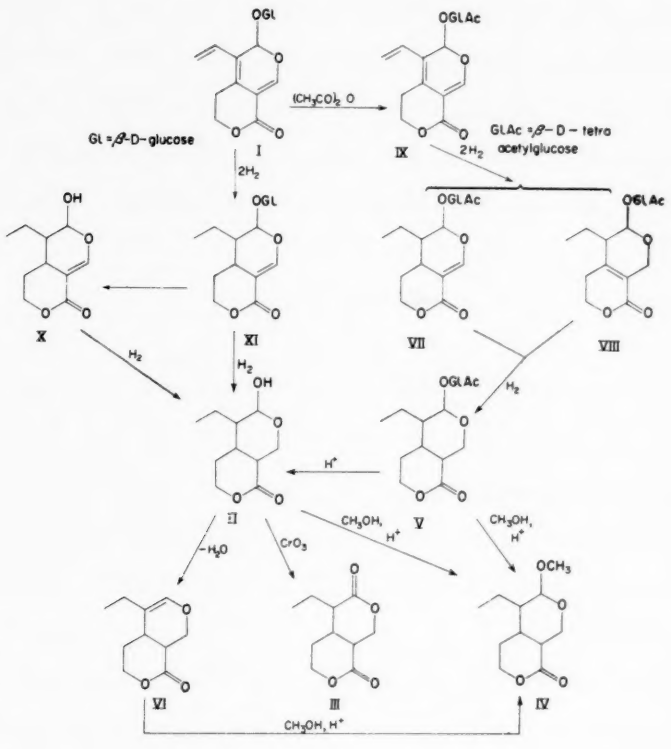


FIG. 1.

and (B) find a complete and independent proof in the NMR spectra.[11]

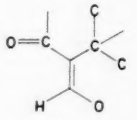
The NMR evidence confirms the presence of an ethyl group in (IV), (VII) and (VIII) [centred triplet at 54.5 and 61 cycles/sec from the TMS reference, for the CH_3- of (IV) and (VII), and of (VIII) respectively].

---

[11] We are greatly indebted to Dr. A. Melera for the measurement of the NMR spectra. Measurements were carried out on a Varian 4302, 60 megacycles spectrophotomer with electronic integrator, in the Research Laboratory of the Varian A.G., Zurich. Samples were dissolved in $CDCl_3$ and TMS was used as internal reference.

The ethyl group is not present in (IX).

The electronic integration shows that (IV) contains five protons on carbon atoms linked to an etheral oxygen, while (III) contains only four such protons. (VII) contains one olefinic proton (centred doublet at 458 cycles/sec with J ~ 2 cycles/sec) which can be attributed to a system such as (G):



(G)

This system is present also in (IX).

The structure with three double bonds attributed to (I) accounts for the absorption maximum at 273 mμ (log ε = 3.84) and for its hydrogenation to (VII) and (VIII).

Also besides the proposed structure has evident biogenetic relationships with another substance extracted from gentianaceae : the alkaloid gentianin.[12]

---

[12] T.R. Govindachari, K. Nagara and S. Rajappa, J. Chem. Soc. 551 (1957).

Tetrahedron Letters No. 24, pp. 13-17, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

DIMERIZATION IN FINKELSTEIN[1] CYCLIZATIONS[2,3]

A. T. Blomquist, Yvonne C. Meinwald

Charles G. Bottomley[4] and Peter W. Martin[5]

Baker Laboratory, Cornell University,

Ithaca, New York

(Received 9 September 1960)

GENERAL concern with the dimethylenecyclobutene system provided a specific interest in the chemistry of dimethylenebenzocyclobutene (I). Since synthesis of the hydrocarbon I from dimethyl benzocyclobutene-1,2-dicarboxylate (II) would be expected to be straightforward,[6] preparation of II was sought *via* a Finkelstein ring closure of α,α'-dibromo-o-phenylene-bis-(methyl acetate) (III).

---

[1] H. Finkelstein, Dissertation, Strasbourg, 1910.

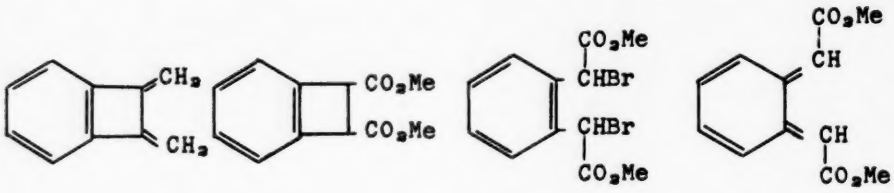
[2] This is the tenth publication concerned with the chemistry of small carbon rings. For the previous paper, see A.T. Blomquist and Y.C. Meinwald, J. Amer. Chem. Soc. 82, 3619 (1960).

[3] This study was supported in part by the National Science Foundation, Grant NSF-G 5923.

[4] American Viscose Fellow, Summer, 1958; Procter and Gamble Fellow, 1959-1960; National Science Foundation Summer Fellow, 1960.

[5] National Science Foundation Undergraduate Research Assistant, Summer, 1960.

[6] A.T. Blomquist and Y.C. Meinwald, J. Amer. Chem. Soc. 82, 3619 (1960).



I II III IV

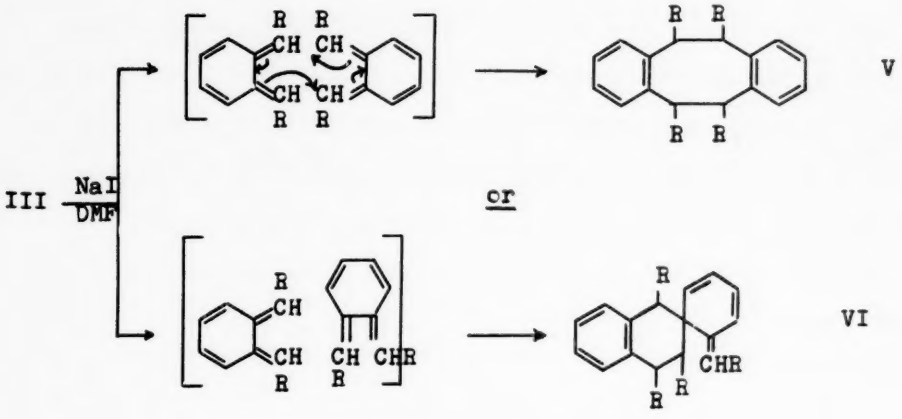
It was observed independently, as established by Cava in the Finkelstein cyclization of α,α,α',α'-tetrabromo-o-xylene to 1,2-dibromobenzocyclobutene,[7] that compound III produced a substituted o-quinodimethane intermediate, compound IV.

Methanolysis at 0° of the product obtained by refluxing o-phenylene-bis-(acetyl chloride)[8] in bromine produced the bromo-ester III (70-80%), m.p. 105.0-106.5°. Reaction of compound III with sodium iodide in dimethylformamide for 48 hr at room temperature gave a 69% yield of a halogen-free tetra-ester, V or VI, m.p. 158.0-158.5°. None of the desired monomeric di-ester II was formed. All of the evidence obtained is in support of structure VI for the tetra-ester, formed by a self Diels - Alder reaction of the o-quinodimethane intermediate IV:

---

[7] M. P. Cava, A. A. Deana and K. Muth, J. Amer. Chem. Soc. 81, 6458 (1959).

[8] J. O. Halford and B. Weissman, J. Org. Chem. 17, 1646 (1952).



The compound absorbs 3 molar equivalents of hydrogen upon catalytic reduction, it possesses a maximum in its ultraviolet spectrum at 327 mμ (log ε 3.97),[9] and in the infrared it has a strong absorption band at 6.21 μ.[10]

Finally, the NMR spectrum of this tetra-ester shows the presence of five vinyl-type hydrogens and that the two adjacent hydrogen atoms on the cyclohexane ring are trans to each other.[11]

The formation of the o-quinodimethane intermediate IV was demonstrated by a trapping experiment. Upon carrying out the Finkelstein reaction in methanol and in the presence of N-phenylmaleimide, the adduct VII, m.p. 229-230°, was isolated in quantative yield. Hydrolysis of the adduct VII,

---

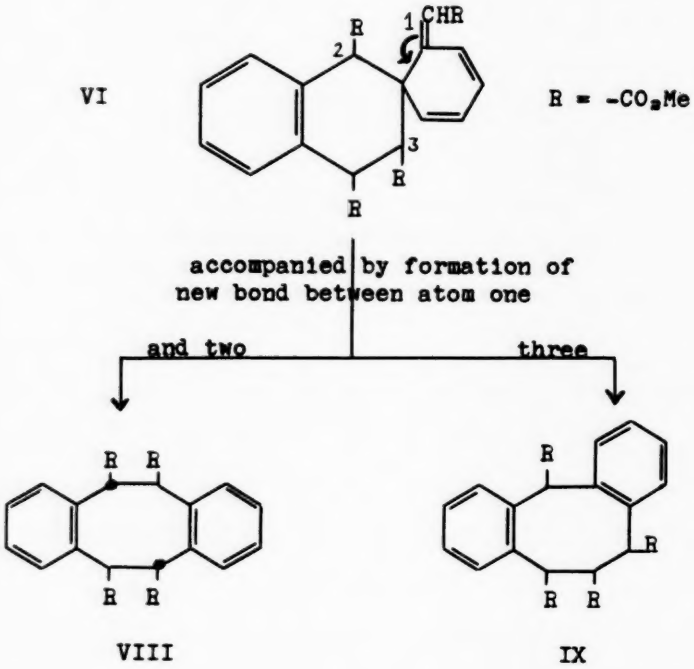
[9] Illustration of a similar chromaphore is "example 20" in L.F. Fieser and M. Fieser, Steroids p. 20. Reinhold, New York (1959).

[10] L.J. Bellamy, The Infra-Red Spectra of Complex Molecules pp. 35-36, John Wiley, New York (1957).

[11] This NMR spectrum together with its interpretation were done by Varian Associates.

followed by decarboxylation and dehydrogenation produced naphthalene.

The tetra-ester VI was unreactive toward the common dienophiles in boiling benzene solution. The compound VI rearranged quantitatively, when heated for 24 hr in boiling xylene, to give an isomeric tetra-ester, m.p. 255.0-255.5°, which had only aromatic unsaturation as shown by its ultraviolet spectrum; λ_{max} 263 mμ, log ε 2.82. The foregoing is consistent with the rearrangement of the "semi-benzene" VI to either of the two dibenzocyclo-öctadienes VIII or IX.[12]



The NMR spectrum of the rearranged tetra-ester shows three groups of

---

[12] Pertinent examples of similar semi-benzene rearrangements are given in a M.S. Newman and L.L. Wood, Jr., J. Amer. Chem. Soc. 81, 4300 (1959); b K. Auwers and K. Ziegler, Liebigs Ann. 425, 217 (1921).

signal peaks which can be assigned to aromatic, methyl ester, and alicyclic hydrogens. The group assignable to alicyclic hydrogens, center ring in VIII, appear as a pair of doublets, indicative of two different hydrogen species strongly spin-coupled. All of this is in full accord with the trans arrangement indicated in VIII and in the preferred conformation proposed for the dibenzocyclooctadiene system in VIII.[13]

Alkaline permanganate oxidation of the tetra-acid, m.p. 259-260°, obtained by acid hydrolysis of the tetra-ester, gives only o-phthalic acid as required by structure VIII.

We have observed the formation dimeric products and also monomeric cyclobutene derivatives in the Finkelstein reaction with α,α'-dibromo-o-ethylbenzylbenzene and α,α'-dibromonaphthalene-2,3-bis-(methyl acetate). Details about these studies will be reported later.

All compounds isolated and described in this report gave correct elemental analyses and molecular weight values.

Acknowledgement - The authors express their gratitude to Mrs. Georgia Fritz for her aid in the determination and interpretation of the NMR spectra of many of the compounds described.

---

[13] W. Baker, R. Banks, D. R. Lyon and F. G. Mann, J. Chem. Soc. 27 (1945).

Tetrahedron Letters No. 24, pp. 18-21, 1960. Pergamon Press Ltd. Printed in Great Britain

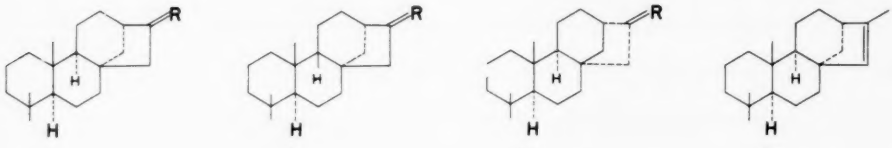
REVISED STRUCTURES FOR MIRENE AND KAURENE

L. H. Briggs, B. F. Cain, R. C. Cambie and B. R. Davis

Department of Chemistry, University of Auckland, New Zealand

(Received 16 September 1960)

IN previous communications[1] structures (Ia), (IIa) and (IIIa) were put forward for phyllocladene, mirene and kaurene respectively. The structure and absolute configuration of phyllocladene was confirmed by relating it to



I

II
a, R=CH_2
b, R=O

III

IV

abietic acid [1c] and later by Grant and Hodges to manool.[2]

Mirene is converted by mild acids into isophyllocladene (IV). There is no simple mechanism for this transformation on the structure suggested for mirene and a model shows that it is the most strained form of isomeric

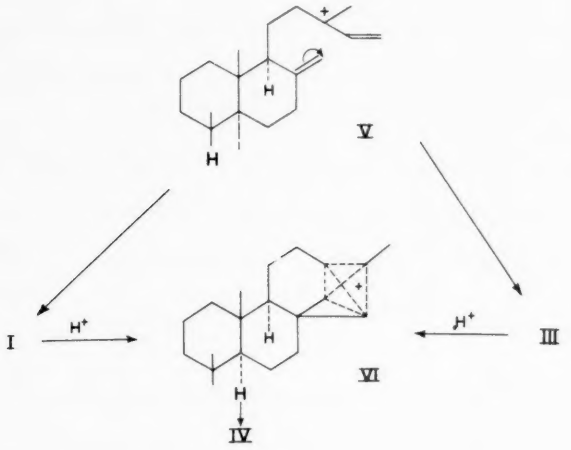
---

[1a] L.H. Briggs, B.F Cain, B.R. Davis and J.K. Wilmhurst, Tetrahedron Letters No. 8, 8 (1959); [b] Ibid. No. 8, 13 (1959); [c] L.H. Briggs, B.F. Cain and R.C. Cambie, Ibid. No. 8, 17 (1959); [d] L.H. Briggs, J. New Zealand Inst. Chem. 23, 92 (1959).

[2] P.K. Grant and R. Hodges, Tetrahedron 8, 261 (1960).

diterpenes of this type.

In the biosynthesis of diterpenes[3] the intermediate (V) would be formed at one stage which can give rise[1b] to isomeric diterpenes (I) and (III) differing only in the disposition of the bridged ring. We now suggest that



mirene be represented by (IIIa) which allows for a more satisfactory explanation for its transformation into isophyllocladene through the intermediate non-classical carbonium ion (VI).

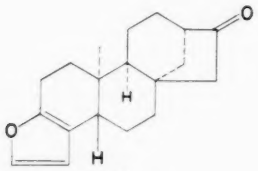
The structure (III a) was previously given to kaurene on the basis of the positive sign of the Cotton effect of the related norketone (III b) but without reference to its rotation. Kaurene, however, occurs in dextro- and laevo-rotatory forms in the essential oils of Podocarpus ferrugineus[4] and

---

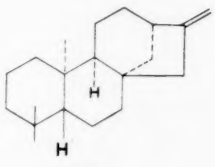
[3] cf. F. Lynen, B.W. Agranoff, H. Eggerer, V. Henning and E.M. Möslein, Angew. Chem. 71, 657 (1959).

[4] L.H. Briggs, R.W. Cawley, J.A. Loe and W.I. Taylor, J. Chem. Soc. 955 (1950).

Agathis australis[5] respectively. The laevorotatory form, $[\alpha]_D$ - 54°, from Agathis australis was used for the preparation of the norketone which has a rotatory dispersion curve* [R.D. in dioxan (c, 0.203): $[\alpha]_{700}$ - 25°; $[\alpha]_{589}$ - 25°; $[\alpha]_{320}$ + 1500°; $[\alpha]_{295}$ - 1000°] characterized by a Cotton effect with the same sign (positive) as and an intensity comparable with those of phyllocladene norketone (I b) and epoxynorcafestadienone (VII)[6] (R.D. peaks at +2240°/322.5 mμ and +2000°/324 mμ respectively). By application



VII



VIII

of the "octant rule",[7] and as we have accumulating evidence that it can be applied in bridged ring systems, we now suggest that (-)kaurene be represented by (VIII), in which the configuration in rings B/C/D is the same as that in phyllocladene and cafestol. In cafestol and (-)kaurene, however, ring B must be present in a boat form.

It is of interest that (-)kaurene has the antipodal form of the normal diterpenoid configuration as exemplified by agathenedicarboxylic acid occurring in the same tree and whose absolute configuration has already been determined.[8] The (+)kaurene, however, in Podocarpus ferrugineus must

---

* We are grateful for Professor Djerassi for this measurement.

5 L.H. Briggs and R.W. Cawley, J. Chem. Soc. 1888 (1948).

6 C. Djerassi, M. Cais and L.A. Mitscher, J. Amer. Chem. Soc. 81, 2386 (1959); R.A. Finnegan and C. Djerassi, Ibid. 82, 4342 (1960).

7 C. Djerassi, Optical Rotatory Dispersion Chap. 13. MsGraw-Hill, New York (1960).

8 W. Klyne, J. Chem. Soc. 3072 (1953).

have the enantiomorphic structure with a normal trans A/B ring junction agreeing with the absolute configuration of the other diterpenoid compounds from the same tree, i.e. ferruginol, sugiol, isopimaric acid, phyllocladene and mirene.

1960

Tetrahedron Letters No. 24, pp. 22-25, 1960. Pergamon Press Ltd. Printed in Great Britain

INTRAMOLECULAR CATALYSIS. FACILITATION OF ALKALINE HYDROLYSIS OF ALICYCLIC 1,2-DIOL MONOESTERS*

S. Morris Kupchan, Peter Slade and Ronald J. Young

Department of Pharmaceutical Chemistry

University of Wisconsin, Madison, Wisconsin

(Received 4 October 1960)

IT is well-established that the hydrolysis of alicyclic axial acetates is accelerated by the presence of an axial hydroxyl group at the 3-position. Earlier work in these laboratories has demonstrated the facilitation in strophanthidin 3-acetate[1,2] and in derivatives of cevine,[1,2] germine,[3] and protoverine.[4] Henbest and Lovell[5] independently showed that the same effect prevailed in some steroid 3,5-diol monoacetates when the acetoxy and hydroxy groups have a 1,3-diaxial relationship. The latter authors attributed the facilitation to hydrogen bonding between the hydroxyl group

---

* Parts I and II in the series are references 1 and 2 respectively.

1 S. M. Kupchan and W. S. Johnson, J. Amer. Chem. Soc. 78, 3864 (1956).

2 S. M. Kupchan, W. S. Johnson and S. Rajagopalan, Tetrahedron 7, 47 (1959).

3 S. M. Kupchan and C. R. Narayanan, J. Amer. Chem. Soc. 81, 1913 (1959).

4 S. M. Kupchan, C. I. Ayres, M. Neeman, R. H. Hensler, T. Masamune and S. Rajagopalan, ibid. 82, 2242 (1960).

5 H. B. Henbest and B. J. Lovell, Chemistry and Industry 278 (1956); J. Chem. Soc. 1965 (1957).

and the ether oxygen of the ester, for which they advanced some infrared evidence.

We report herein that the base-catalyzed hydrolysis of some alicyclic acetates is accelerated by the presence of an adjacent hydroxyl group. Our first results were obtained with a steroid-5,6-diol monoacetate. When cholestane-5α,6α-diol 6-monoacetate[6] was heated under reflux with potassium carbonate in aqueous methanol and benzene, 81% of the 5,6-diol was isolated after 1 h., and 93% after 2 h. The same treatment of cholestane-6α-ol acetate[6] led to formation of only 25% of cholestane 6α-ol after 2 h. Since variation of the 5α-substituent would have been difficult in this series, further studies were undertaken with various derivatives of cholestane-3β,4β-diol.

Subsequent hydrolyses were performed at 30° in aqueous dioxane containing sodium hydroxide. The amount of base consumed was measured by removing aliquots at intervals and titrating with standard hydrochloric acid. The compounds studied are listed in Table 1. There was some departure from strictly second order kinetics after the reactions had proceeded to some extent: when

Table 1. Second Order Rate Constants for Alkaline Hydrolysis in 20% Aqueous Dioxane at 30°

Compound	10^3k(l. mole^{-1} sec^{-1})
cholestane-3β-ol acetate	2.7
cholestane-3β,4β-diol 3-monoacetate[7]	22
cholestane-3β,4β-diol 4-monoacetate[8]	24
3β-methoxycholestane-4β-ol acetate[9]	1.3

[6] D. N. Jones, J. R. Lewis, C. W. Shoppee and G. H. R. Summers, J. Chem. Soc. 2876 (1955).

this occurred. the approximate second order rate constants were calculated from the slopes of the initial portions of the kinetic plots. The constants thus obtained are probably accurate to within 10%.[10]

The hydrolysis of the 3-β-acetate is thus accelerated eight or nine-fold when a 4β-hydroxy group is introduced into the molecule. The greater extent of facilitation than that previously found for an aliphatic 1,2-diol monoester[11] is readily explicable in terms of a more effective interaction between the hydroxy and acetoxy groups in the rigidly fixed alicyclic case. In view of the migration of the acetate group from the 3 to the 4 position on slightly alkaline alumina,[8] alkaline hydrolysis of the 3β,4β-diol 3-acetate may proceed via intermediate formation of the 4-acetate.

---

7 S. Liebermann and D. K. Fukushima, J. Amer. Chem. Soc. 72. 5211 (1950).

8 Prepared by treatment of cholestane-3β,4β-diol 3-acetate with slightly alkaline alumina (Woelm, "neutral", Activity I). The identity of the compound was proved by hydrolysis to the known cholestane 3β,4β-diol, and by oxidation to cholestane-3-one-4β-ol acetate (authentic specimen kindly supplied by Dr. K. L. Williamson; see K. L. Williamson, Ph.D. Dissertation, University of Wisconsin. 1960). Satisfactory analytical and spectral data were obtained for new compounds reported herein.

9 Prepared from the corresponding hydroxy-acetate by methylation with diazomethane in the presence of fluoroboric acid. Cf. M. Neeman, M. C. Caserio, J. D. Roberts and W. S. Johnson, Tetrahedron 6, 36 (1959).

10 We thank Professor T. Higuchi for valuable discussion of the kinetic data.

11 Ethylene glycol monoacetate has been shown to be hydrolyzed about 2 1/2 times faster than ethyl acetate in aqueous solution, M. H. Palomaa, Ann. Acad. Sci. Fennicae A 5, No. 4, 1 (1914), cf. Chem. Zentr. 89. I, 1143 (1918); H. Olsson, Z. physik. Chem. 133, 235 (1928).

1960

In the case of the diol-4-monoacetate, it was found that replacement of the 3-hydroxy group by a methoxy group (with a very similar inductive effect) caused the rate of hydrolysis of the 4β-acetate to be retarded 19-fold. This strongly supports the view that the hydroxyl group plays an important role in the facilitation of hydrolysis noted in the hydroxy esters, probably through hydrogen bonding. Further studies on the nature of the facilitation are in progress.

This investigation was supported in part by a grant (H-2275 (C4)) from the National Institutes of Health, U.S. Public Health Service. The receipt of a Wellcome Research Travel grant, awarded by the Wellcome Trust, is gratefully acknowledged by P. S.

Tetrahedron Letters No. 24, pp. 26-29, 1960. Pergamon Press Ltd. Printed in Great Britain

PHENYLCARBENE FROM BENZYLCHLORIDE AND N-BUTYLLITHIUM

Gerhard L. Closs and Liselotte E. Closs

Department of Chemistry, The University of Chicago
Chicago 37, Illinois

(Received 17 October 1960)

Several earlier investigators have shown that the action of strong bases on benzylic halides normally does not lead to the formation of carbenes.[1] We wish now to present evidence demonstrating that under certain conditions phenylcarbene can be produced *via* α-elimination from benzylchloride.

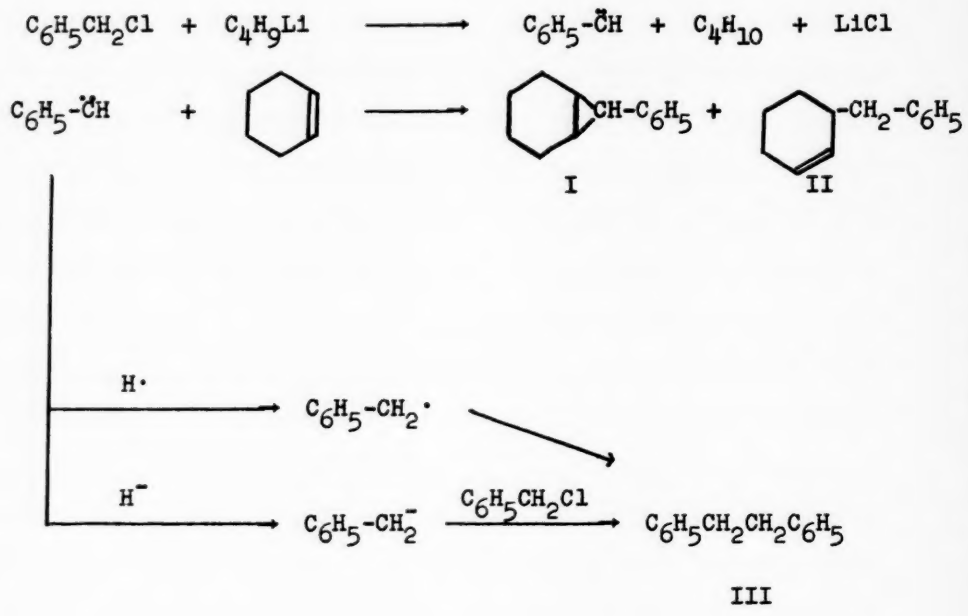
N-Butyllithium in ether was slowly added to a solution of benzylchloride in excess cyclohexene at 10°. Separation of the reaction mixture by distillation and subsequent chromatography gave 14% of 7-phenylbicyclo(4.1.0)heptane (I) (anal. found: C 90.66; H 9.48), 19% of 3-benzylcyclohexene (II) (anal. found: C 90.70; H 9.43), 14% of 1,2-diphenylethane (III) and 30% of amylbenzene (IV). Structures of I and II have been confirmed by chemical and spectral evidence. Thus both compounds are reduced

1 M. S. Kharasch, W. Nudenberg and E. K. Fields, J. Am. Chem. Soc. 66, 1276 (1944); L. A. Pinck and G. E. Hibert, ibid. 68, 377 (1946); C. R. Hauser, W. R. Brasen, P. S. Skell, S. W. Kantor and A. E. Brodhag, ibid. 78, 1653 (1956).

1960

catalytically to benzylcyclohexane. The infrared spectrum of II exhibits double bond stretching vibration at 1655 cm^{-1} and the nuclear magnetic resonance (n.m.r.) spectrum reveals the presence of two olefinic protons (broad peak at 47 c.p.s. relative to external benzene at 40 m.c.). Likewise, the attachment of the benzyl group at the 3 position of the cyclohexane ring is evident from the n.m.r. spectrum which shows resonance of 3 allylic protons. Both infrared and n.m.r. spectra of I provide no evidence for double bonds and are consistent with the cyclopropane structure. The two possible stereoisomers of I, epimeric at carbon atom 7, are both formed and the n.m.r. spectrum of the mixture shows two bands with a ratio of integrated intensities of 1:2 attributed to the phenyl protons of the isomers. Repeated chromatography resulted in partial separation of the epimers as evidenced by different intensity ratios of these bands in the spectra of the various chromatography fractions.

The presence of I among the reaction products is interpreted as evidence for the formation of phenylcarbene. The mechanism of the formation of II needs some further study, although it is strongly suspected that phenylcarbene serves as precursor to this product as well. However, at this point it cannot be decided whether II originates from an apparently selective insertion of the carbene into the allylic carbon-hydrogen bonds or is a product of a consecutive rearrangement of I.



1,2-Diphenylethane (III) had previously been isolated as major product from the reaction of benzylchloride with butyllithium.[2] It had been suggested that this compound was formed via halogen-metal interchange leading to butylchloride and benzyllithium. The latter was assumed to couple with excess benzylchloride to give III. This reaction scheme cannot be upheld in view of our finding that only traces of butylchloride are produced in this reaction as shown by vapor phase chromatography of the reaction mixture. It appears more likely that III also originates from phenylcarbene

---

2 H. Gilman and A.H. Haubein, J. Am. Chem. Soc. 66, 1515 (1944).

which by hydride or hydrogen abstraction from the solvent may produce phenylmethide ion or benzyl radical respectively. Both these hypothetical intermediates can be expected to lead to the observed product. This hypothesis is supported by the observation that photochemically generated diphenylcarbene gives rise to the formation of the equivalent product, 1,1,2,2-tetraphenylethane.[3]

3 W. Kirmse, L. Horner and H. Hoffmann, Ann. 614, 19 (1958).

Tetrahedron Letters No. 24, pp. 30-36, 1960. Pergamon Press Ltd. Printed Great Britain

O^{18} TRACER EVIDENCE OF THE TERMINATION MECHANISM IN THE AUTOXIDATION OF CUMENE

T. G. Traylor and P. D. Bartlett

Department of Chemistry, Harvard University, Cambridge, Massachusetts

(Received 20 October 1960)

The chain terminating step in many autoxidations is known from the non-dependence of rate on oxygen pressure to be an interaction of two alkylperoxy radicals.[1 - 4] Reaction (1) is considered to occur with tertiary $RO_2\cdot$ radicals[5], but the indicated re-formation of an oxygen molecule could not be demonstrated directly.

$$2\ ROO\cdot \longrightarrow O_2 + ROOR \qquad (1)$$

Also it has been unknown whether the two oxygen atoms which form the free oxygen molecule originate from the same alkylperoxy radical[6] or from different ones[5,7].

With the availability of 99.4% oxygen-18 in the form of molecular oxygen[8], (called here O* O*) a direct experimental answer to this question is now possible. Cumene, autoxidized with a known mixture of

---

[1] E. J. Bowen and E. L. Tietz, J. Chem. Soc. 1930, 234.

[2] H. L. J. Bäckström, Z. phys. Chem. B 25, 99 (1934).

[3] C. H. Bamford and M. J. S. Dewar, Proc. Roy. Soc. A 198 252 (1949).

[4] C. Walling, Free Radicals in Solution. John Wiley and Sons, New York, 1957, pp. 418-427, 442-447.

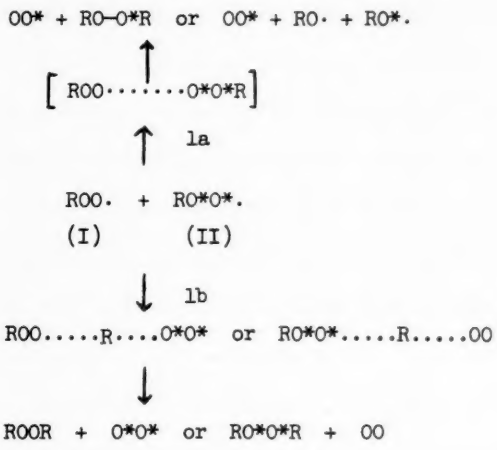
[5] G. A. Russell, J. Amer. Chem. Soc. 79, 3871 (1957).

[6] C. E. Boozer, B. W. Ponder, J. C. Trisler, and C. E. Wightman, ibid. 78, 1506 (1956).

[7] H. S. Blanchard, ibid. 81, 4548 (1959).

[8] Obtained from the Isotope Department, Weizmann Institute of Science, Rehovoth, Israel.

00 and 0*0*, must form cumylperoxy radicals (I and II) each containing two identical oxygen atoms.



Reaction mode 1a, involving head-to-head reaction of I and II, must then produce the unsymmetrical oxygen -34 molecule, 00*, whereas any displacement mechanism such as 1b will produce only O_2^{32} (00) and O_2^{36} (0*0*), without resulting equilibration with O_2^{34}.

Experimental conditions were chosen under which the organic products have already been investigated by Blanchard[7]. In a typical run, a reaction flask connected by a glass stopcock to an evacuable sampling lock was charged on the vacuum line with 41.3 ml of a solution of cumene (1.36 M) in chlorobenzene containing azobis-isobutyronitrile (AIBN) at a concentration of 0.0952 M. Into the 82-ml gas space ordinary oxygen, oxygen-36 (0*0*), and argon were introduced in the ratio of 25.40: 0.73: 4.36. The reaction was conducted in a thermostat at

59.85°C with vigorous magnetic stirring. Samples (0.66 ml) of gas were taken at time intervals as shown in Table 1, and the intensities of the peaks at masses 28, 32 34, 36, and 40 were recorded using a Consolidated Type 21-103C mass spectrometer. The analyses beyond the first were all evaluated relative to the argon which was taken as constant at 4.36×10^{-4} moles, based on the original composition at 25°. The amount of 00* (oxygen-34) initially present (0.113×10^{-4} moles) is close to that (0.112×10^{-4} moles) calculated from the natural abundance (0.204%) of O^{18} in ordinary oxygen, confirming the reported purity of the 0*0*. From Table 1 it is evident that nitrogen is being evolved and that 00* (O_2^{34}) is appearing.

TABLE 1

Gas Composition During the Autoxidation of 1.36 M Cumene in Chlorobenzene Containing 0.0952 M AIBN at 59.85° (Run 1)

Time (sec)	Quantity of Gas in Moles x 10^4					
	N_2^{28}	O_2^{32} (x)	O_2^{34} (y)	O_2^{36} (z)	w= x+y+z	O^{18} Atom %
0	0.422	25.29	0.113	0.731	26.13	3.02
495	0.497	24.65	0.119	0.669	25.44	2.86
1200	0.639	23.64	0.133	0.666	24.44	2.99
2280	1.333	20.94	0.152	0.580	21.67	3.02
3750	1.95	18.09	0.173	0.485	18.75	3.05
5640	2.80	14.40	0.180	0.366	14.95	3.07
9240	4.23	7.99	0.158	0.176	8.424	3.07
13560	6.05	1.18	0.03	0.02		
16920	7.36	.14				
34560	13.8	.09				

We found no equilibration among the species 00, 0*0*, and 00* on long

standing, or during photooxidation of rubrene, or from thermal decomposition of rubrene peroxide or in presence of decomposing unlabeled t-butylhydroperoxide. Therefore, the appearance of O_2^{34} (OO*) is best accounted for as indicating the formation of oxygen molecules by path 1a in the course of chain termination. This interpretation is supported by the kinetic analysis of the results.

Under the experimental conditions nitrogen is evolved at a constant rate R_i and total oxygen is absorbed at a constant rate b. (From R_i we estimate a first-order rate constant of 1.20×10^{-5} sec $^{-1}$ for AIBN decomposition, to be compared with Russell's value[5] of 1.15×10^{-5}). Assuming the generally accepted[4] mechanism for cumene autoxidation, plus path 1a for chain termination, we can derive Equations 2 and 3 which are convenient for determining the rates C_w and G_w of consumption and generation, respectively, of oxygen during the experiment.

$$\ln \frac{f_y - (M_y)_o}{f_y - M_y} = \frac{G_w}{b} \ln \frac{w_o}{w} \qquad (2)$$

$$\ln \frac{z_o}{z} = \frac{C_w}{b} \ln \frac{w_o}{w} \qquad (3)$$

Here f_y is the probability that a terminating collision of two RO_2 radicals will be between a labeled and an unlabeled radical. This probability is taken as equal to $2\alpha(1-\alpha)$, where α is the atom-fraction of O^{18} in the total oxygen, and isotope effects are neglected. Total oxygen is $w = x+y+z$ (see Table 1) and M_y is the mole-fraction of O_2^{34} (OO*) in the oxygen.

Equations 2 and 3 afford independent determinations of G_w and C_w

from the measurements of masses 34 and 36 as functions of total oxygen. Since $b = C_w - G_w$, these results can be checked against each other. Figures 1 and 2 show the plots of Equation 2 and 3 for the run described and Table 2 lists the quantities entering into these equations and derived from them.

If AIBN produces free radicals with an efficiency e, and if β oxygen molecules are re-formed for each pair of kinetic chains which terminates, then $G_w = e\beta R_i$. The values of $e\beta$

TABLE 2

Kinetic Analysis of Data of Table 1

$\alpha = .0302$

$f_y = .0588$

$b = 1.98 \times 10^{-7}$ moles/sec

"y slope" $= \frac{G_w}{b} = .275$

"z slope" $= \frac{C_w}{b} = 1.244$

C_w from "z slope" $= 2.46 \times 10^{-7}$

$G_w = C_w - b = .48 \times 10^{-7}$

G_w from "y slope" $= .54 \times 10^{-7}$

$e\beta = \frac{G_w}{R_i}$

from "y slope" = 1.30

from "z slope" = 1.15

from the "y" and "z" slopes are 13% apart, and agree approximately

1960

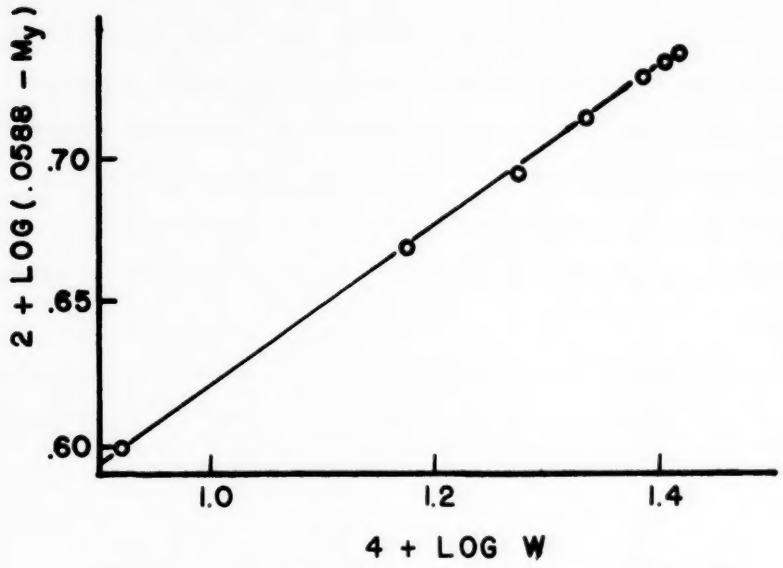


Figure 1. Plot of Equation 2 for O_2^{34} data.

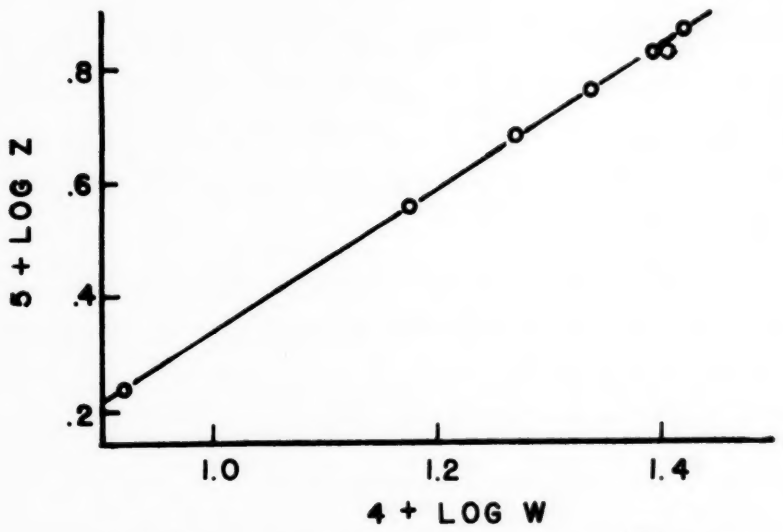


Figure 2. Plot of Equation 3 for O_2^{36} data.

(1.15 and 1.30 vs. 1.11) with the value estimated by Blanchard[7] from determination of the non-hydroperoxide products. Thus there is enough 00* produced in our experiments to account for <u>all</u> chain termination as proceeding by reaction path 1a, and likewise for that extra oxygen evolution, deduced by Blanchard, which is accompanied by the formation of cumyloxy radicals and acetophenone molecules rather than by chain-terminating R_2O_2 formation. The facts are well accommodated by the sequence

$$2\ RO_2 \longrightarrow ROOOOR \qquad (4)$$

$$ROOOOR \longrightarrow O_2 + \left[2RO\cdot\right] \qquad (5)$$

$$\left[2RO\cdot\right] \longrightarrow ROOR \qquad (6a)$$

$$\left[2RO\cdot\right] \longrightarrow CH_3COC_6H_5 + CH_3\cdot \qquad (6b)$$

If we adopt a value of 0.60 for e, as Blanchard does, then our two values of β are 1.92 and 2.17. If the species $\left[2RO.\right]$ of Equations 5 and 6 is a radical pair in a solvent cage, then its efficiency of escape is 48-54%, a normal value. Actually, the circumstances of Reaction 5 are enough like those of the original breakdown of AIBN so that the fate of the radical pair produced might be determined in an entirely similar way by the cage effect.

Details of the experiments over a range of conditions, kinetic derivations, and application of the method to other cases, will be described in a forthcoming publication.

We thank the National Institutes of Health for support of this work through a fellowship and a research grant.

1960

Tetrahedron Letters No. 25,pp. 1-3, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

PHOTODIMERIZATION OF SOME α,β-UNSATURATED LACTAMS[1]

Edward C. Taylor and W. W. Paudler

Frick Chemical Laboratory, Princeton University,

Princeton, New Jersey

(Received 28 October 1960)

THE dimerization of activated olefins by irradiation with ultraviolet light is one of the oldest and most widely-studied reactions in photochemistry.[2,3] There are, however, no reports of the action of ultraviolet light on α,β-unsaturated lactams. We wish to report that N-methyl-2-pyridone (b.p. 121°/10 mm, λ_{max}^{EtOH} 302 mμ, ε = 5700) is rapidly converted by ultraviolet light to a solid dimer (m.p. 222.0-222.5°; Found: C, 66.25; H, 6.4; N. 12.95. mol. wt. 226. λ_{max}^{EtOH} 312 mμ, ε = 100. Calc. for $C_{12}H_{14}N_2O_2$: C, 66.0; H, 6.5; N, 12.8. mol. wt. 218), which reverts to N-methyl-2-pyridone upon heating above its melting point. It is evident from inspection of the ultraviolet spectra that the α,β-unsaturated system present in the monomer is no longer present in the dimer, which thus may be represented as I or Ia. The presence

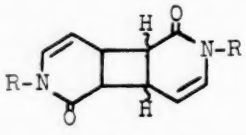
---

[1] This work was supported by a research grant (CY-2551) to Princeton University from the National Cancer Institute of the National Institutes of Health, Public Health Service.

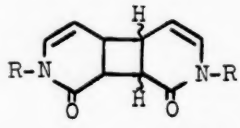
[2] A. Schönberg, Präparative organische Photochemie p. 30. Springer Verlag, Berlin (1958).

[3] P. de Mayo in Advances in Organic Chemistry: Methods and Results (Edited by R. Raphael, E.C. Taylor and H. Wynberg) p. 367. Interscience, New York (1960).

of the isolated double bonds in I (or Ia) was readily confirmed by hydrogenation to a tetrahydro derivative (m.p. 285-286°. Found: C, 64.85; H, 8.2; N, 12.4. λ_{max}^{EtOH} only end absorption about 220 mμ. Calc. for $C_{12}H_{18}N_2O_2$: C, 64.8; H, 8.2; N, 12.6.) and by conversion to a diepoxide (m.p. 324-326°. Found: C, 57.7; H, 5.8; N, 11.3. Calc. for $C_{12}H_{14}N_2O_4$: C, 57.6; H, 5.6; N, 11.2). Determination of the dipole moment of the dimer as 0.07 D (in $HCCl_3$) clearly establishes I as the correct structure.



I, R = CH_3
II, R = H

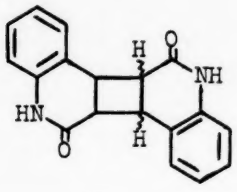


Ia, R = CH_3

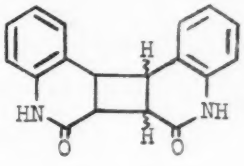
Irradiation of 2-pyridone (m.p. 106-107°) in aqueous solution yields a dimer (II) (m.p. 225.5-227.5°. Found: C, 62.8; H, 5.3; N, 15.0. Calc. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.3; N, 14.7) which upon methylation with dimethylsulfate and alkali gives I, identical in every respect with the product obtained directly from N-methyl-2-pyridone.

The use of this photodimer as a synthetic intermediate for the preparation of both pyridine and cyclobutane derivatives is under active investigation; results will be reported independently.

Irradiation of a suspension of N-methyl-2-quinolone (m.p. 74°) in cyclohexane or in water yields a dimer (m.p. 211.5-212°. Found: C, 75.6; H, 5.8; N, 9.0; mol. wt. 272. Calc. for $C_{20}H_{18}N_2O_2$: C, 75.4; H, 5.7; N, 8.8; mol. wt. 318) which, because of its dipole moment of 4.62 D (in $HCCl_3$) must be assigned structure IIIa rather than III. Heating reconverts it rapidly and quantitatively to N-methyl-2-quinolone.



III



IIIa

1960

The different orientations of the dimers I and IIIa is undoubtedly due to the fact that N-methyl-2-pyridone was irradiated either as the neat liquid or in homogeneous solution in ethanol, while N-methyl-2-quinolone was irradiated in suspension. Similar cases of dependence of the course of dimerization on the physical state of the compound being irradiated are well-known.[2,3]

Tetrahedron Letters No. 25, pp. 1-8, 1960. Pergamon Press Ltd. Printed in Great Britain

An Octahydrodimethanonaphthyl Non-Classical Homocyclopropenyl Cation[1]

S. Winstein and Robert L. Hansen

Dept. of Chemistry, University of California, Los Angeles, Calif.

(Received 31 October 1960)

In connection with non-classical carbonium ions, system II was of interest for comparison with the anti-7-norbornenyl[2] analog I and the unsaturated endo-endo system[3] III. One could anticipate great anchimeric acceleration of ionization of suitable II-derivatives, with formation of a relatively unique homocyclopropenyl variety of carbonium ion IV.

Alcohol II-OH has now been prepared through the Diels-Alder condensation of cyclopentadiene with anti-7-norbornenol[2] tetrahydropyranyl ether[4], b.p. 89-93° (2.5 mm.), $n^{25}D$ 1.4865, under nitrogen at 215° in the presence of diphenyl amine. Careful hydrolysis of the fraction of the product with b.p. 105-130° (2.5 mm.), followed by recrystallization and sublimation, leads to alcohol[4] II-OH, m.p. 108-109°; p-nitrobenzoate[4], m.p. 131-132°; p-toluenesulfonate[4], m.p. 102.5-103°; p-bromobenzenesulfonate[4] II-OBs, m.p. 96-97° (dec.).

---

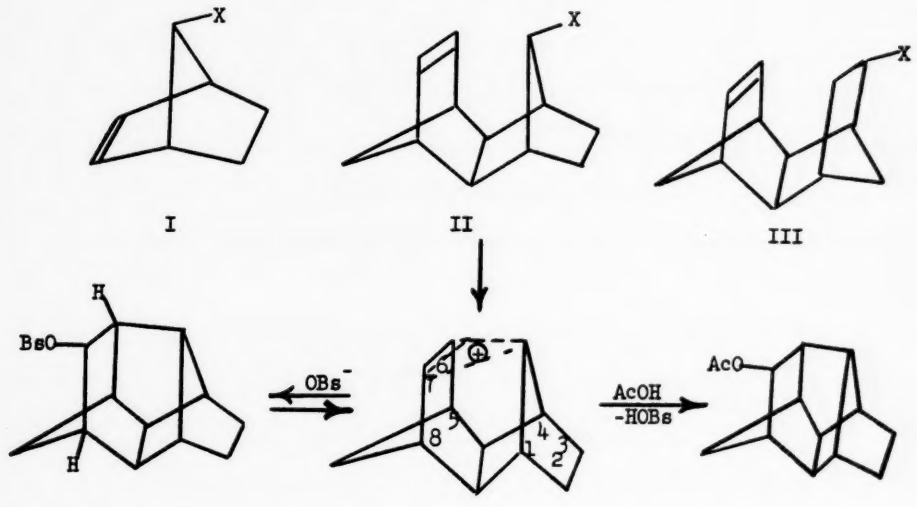
[1] Research sponsored by the Office of Ordnance Research, U.S. Army.

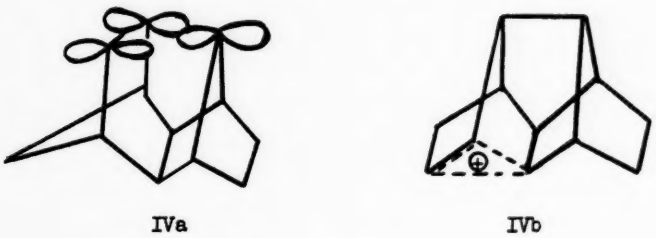
[2] (a) S. Winstein, M. Shatavsky, C. Norton and R. B. Woodward, J. Am. Chem. Soc. 77, 4183 (1955); (b) S. Winstein and M. Shatavsky, ibid. 78, 592 (1956).

[3] P. Bruck, D. Thompson and S. Winstein, Chemistry and Industry 590 (1960).

[4] A satisfactory C,H-analysis was obtained for this and the other indicated new compounds here reported.

1960





Bromobenzenesulfonate II-OBs is very reactive in acetolysis, the first order rate constant being $(2.38 \pm 0.02) \times 10^{-4}$ sec.$^{-1}$ at 25.0°. Ion pair return accompanies the acetolysis, 12% of a less reactive bromobenzenesulfonate being formed. The acetolysis rate constant of this latter isomer, measured after the solvolysis of II-OBs was complete, was $(8.9 \pm 0.3) \times 10^{-5}$ sec.$^{-1}$ at 75.0°.

The solvolysis product from II-OBs is saturated and consists of a single compound as indicated by vapor phase chromatographic examination

of the acetate (A-OAc) and the derived alcohol[4] (A-OH), m.p. 80.0-81.5°. The acetolysis rate constant of the bromobenzenesulfonate[4] (A-OBs) of this latter alcohol, m.p. 112.5-113.8°, is identical with that of the isomer formed from II-OBs during its acetolysis, being (9.12 ± 0.08) x 10^{-5} sec.$^{-5}$ at 75.0° and (3.85 ± 0.04) x 10^{-6} sec.$^{-1}$ at 50.4°. Further, no visible rearrangement occurs in acetolysis of A-OBs, only A-OAc being regenerated.

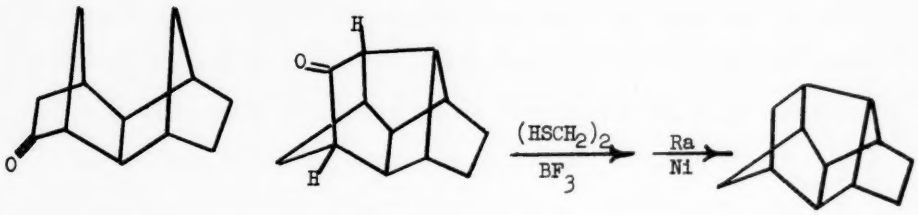
It is quite clear that A-OAc and A-OBs, the saturated isomers of II-OAc and II-OBs formed during acetolysis of II-OBs, have the V-structure. Thus, bromobenzenesulfonate A-OBs is recovered unchanged from an 18 hour treatment with potassium t-butoxide in refluxing benzene, no elimination being observed. Under these conditions, the olefinic group is introduced smoothly into other bicycloheptyl derivatives[5]. Further, the A-ketone from oxidation of A-OH showed no detectable deuterium exchange on treatment with 0.05 M sodium methoxide in 95% tetrahydrofuran-deuterium oxide for 51 hours at 50°. Under these conditions, ketone VI, obtained by oxidation of the corresponding alcohol[6], exchanges rapidly. The behavior of A-OBs and A-ketone is in accord with the position of the OBs and ketone groups in structures V-OBs and VII, since these would require a double bond or the enolate ion to be formed at a bridgehead. Finally, the carbon skeleton of V is confirmed by conversion of ketone VII to hydrocarbon VIII. Treatment of ketone VII with ethylene dithiol under forcing conditions converts it to an ethylene dithioketal. By Raney nickel desulfurization the latter is reduced to a saturated hydrocarbon whose infrared spectrum and vapor phase chromatographic behavior are

---

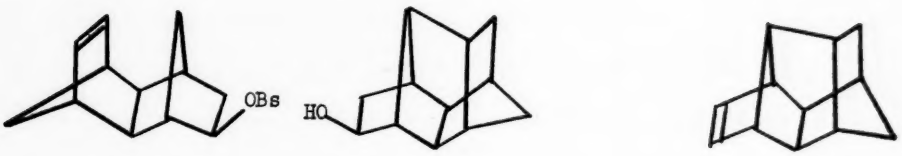
[5] (a) S. Winstein and E. T. Stafford, J. Am. Chem. Soc. 79, 505 (1957); (b) S. Winstein and C. Ordronneau, ibid. 82, 2084 (1960); (c) E. T. Stafford, F. Gadient and R. Hansen, unpublished work.

[6] S. B. Soloway, J. Am. Chem. Soc. 74, 1027 (1952).

1960



VI VII VIII



IX X XI

identical with those of hydrocarbon[4] VIII obtained by hydrogenation of olefin[7] XI. The latter olefin is the one related to the "twisted" alcohol[3,7] X, one of the important rearranged saturated products of solvolysis of system[3] III or bromobenzenesulfonate[7] IX.

While rate of ionization in the II-system is not up to that observed[3] with III, it is nearly the same as that for anti-7-norbornenyl[2] (I). The rate constants observed with II-OTs or II-OBs are lower than those for the anti-7-norbornenyl analogs by a factor of only ca. 4. Thus, II-OBs ionizes more rapidly than 7-norbornyl[2,5c] bromobenzenesulfonate by the very large factor of 10^{11}.

The anchimerically accelerated ionization of II-OBs presumably leads to the non-classical cationic structure IV, which may be regarded as a cyclopropenyl cation in which 3-carbon segments have been inserted in each of two sides. The homoconjugation in ion IV, involving electron delocali-

---

[7] L. de Vries and S. Winstein, ibid. in press.

zation across intervening carbon atoms[8], is wave-mechanically analogous to that in cyclopropenyl[9], except that 1,3- as well as 1,2-overlap and exchange integrals are involved. As illustrated in IVa, the axes of the p-orbitals on the three cationic carbon atoms are each turned ca. 90° from their orientation in cyclopropenyl. The situation is quite analogous in the non-classical cation described by Leal and Pettit[10].

The simplest mechanism of formation of the single solvolysis product from II-OBs and V-OBs involves solvent attack on carbon atoms C-6 and C-7 of ion IV, rather than on a further rearranged species such as IVb. This point is subject to stereochemical check. so the stereochemistry of solvolysis of V-OBs is being examined.

---

[8] (a) M. Simonetta and S. Winstein, ibid. 76, 18 (1954); (b) S. Winstein, ibid. 81, 6524 (1959).

[9] (a) E. Hückel, Z. Physik 70, 204 (1931); (b) J. D. Roberts, A. Streitwieser, Jr., and C. M. Regan, J. Am. Chem. Soc. 74, 4579 (1952); (c) W. G. Woods, R. A. Carboni and J. D. Roberts, ibid. 78, 5653 (1956).

[10] G. Leal and R. Pettit, ibid. 81, 3160 (1959).

Tetrahedron Letters No. 25, pp. 9-16, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

PREPARATION AND BEHAVIOR OF SIMPLE QUINONE METHIDES

Leo J. Filar

Research Center, Hercules Powder Company, Wilmington, Delaware

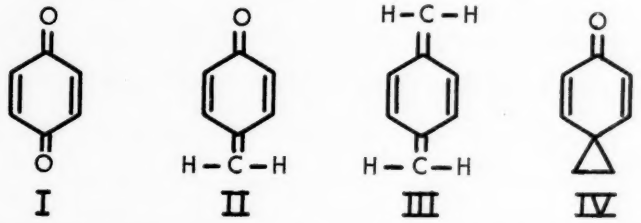
and

S. Winstein

Dept. of Chemistry, University of California, Los Angeles, Calif.

(Received 2 November 1960)

METHYLENE cyclohexadienones, or quinone methides, e.g., the simplest member II, are of considerable theoretical interest in the same context with benzoquinone (I) and p-xylylene[1,2] (III).



I II III IV

Therefore, they have been the subject of numerous investigations and discussions extending over many years.[3] Certain substituted methides,

---

[1] M. Diatkina and J. Syrkin, Acta Physicochim. URSS 21, 23, 921 (1946); C. A. Coulson, D. P. Craig, A. Maccoll, and A. Pullman, Discuss. Faraday Soc. 2, 36 (1947); A. Pullman, G. Berthier, and B. Pullman, Bull. Soc. Chim France 15, 450 (1948).

[2] L. A. Errede and M. Szwarc, Quart. Revs. 12, 301 (1958).

[3] See R. W. Martin The Chemistry of Phenolic Resins, p. 139, Wiley, N. Y. (1956); and K. Hultzsch, Chemie der Phenolharze, p. 63, Springer, Berlin (1950).

such as 10-methylene anthrone,[4] are well-authenticated compounds. With fewer substituents on the ring, the methides become much less stable, and attempts to isolate the simpler ones, such as the 2,6-dimethyl compound, have led only to dimeric products.[5] With the 2,6-di-t-butyl compound, stable products have resulted only when the methylene group was further substituted.[6] The recently reported o-quinone methide,[7] was unstable even at high dilution at room temperature.

By the general spectroscopic approach employed previously in the study of spiro[2,5]octa-1,4-diene-3-one (IV),[8] it has been possible to study the preparation and behavior of the relatively simple and quite unstable quinone methides in dilute solution. The results obtained are very instructive, and we present some of them in the present communication.

We have observed that dilute solutions of quinone methides may be prepared from either the corresponding benzyl halide or the parent phenol. Thus, 2,6-dimethyl-4-methylene-2,5-cyclohexadienone (VI) is obtained in 10^{-5} to 10^{-3} M solution from treatment of a hydrocarbon solution of 3,5-dimethyl-4-hydroxybenzyl chloride (Va) with a base, such as triethylamine. Analogously, 2,6-di-t-butyl-4-methylene-2,5-cyclohexadienone may be obtained from the appropriate benzyl bromide.[9]

---

[4] E.g., H. Heymann and L. Trowbridge, J. Am. Chem. Soc. 72, 84 (1950).

[5] K. Fries and E. Brandes, Ann. 542, 48 (1939); H. von Euler, E. Adler, J. O. Cedwall, and O. Törngren, Arkiv. Kem. Mineral Geol. 15A, No. 11 (1942).

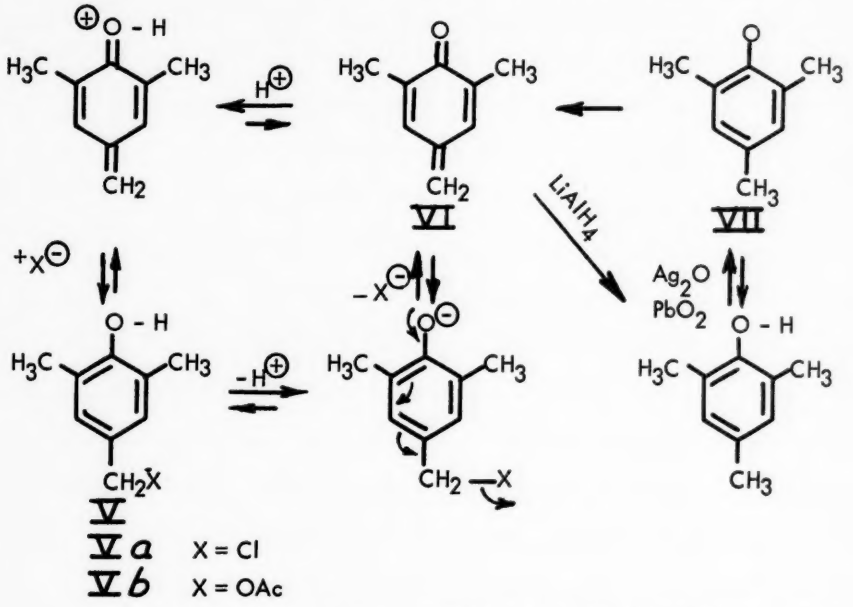
[6] C. D. Cook and B. E. Norcross, J. Am. Chem. Soc. 78, 3797 (1956). Ibid. 81, 1176 (1959).

[7] P. D. Gardner, H. Sarrafizadeh R., and R. L. Brandon, Ibid. 81, 5515 (1959).

[8] S. Winstein and R. Baird, Ibid. 79, 756, 4238 (1957).

[9] C. D. Cook, N. G. Nash, and H. R. Flanagan, Ibid. 77, 1783 (1955).

Alternatively, the quinone methide VI was obtained by shaking a solution of mesitol with silver oxide. Analogously, the 2,6-di-t-butyl analog was obtained from oxidation of the parent phenol with lead dioxide.

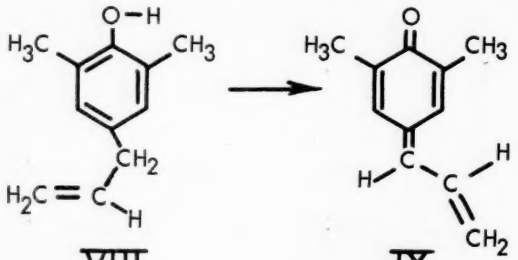


The formation of quinone methides by oxidation of the corresponding phenols presumably proceeds through aryloxy radicals, e.g., VII. In reporting on the behavior of such radicals, Cook and Norcross[6] have described a second order disproportionation of the 2,6-di-t-butyl-4-isopropylphenoxy radical to the corresponding phenol and quinone methide. On the other hand, Bennett[10] has reported first order decay of the corresponding 4-methyl and 4-ethyl analogs. Under the present conditions, with excess metal oxide, it is not clear how aryloxy radical is converted to quinone methide.

---

[10] J. E. Bennett, Nature 186, 385 (1960).

An interesting extension of the oxidation method of producing quinone methides involves 2,6-dimethyl-4-allylphenol (VIII). Treatment of the latter compound with silver oxide yields a material whose properties are consistent with the quinone methide structure IX.



VIII IX

The structure of the quinone methides is clear from their ultraviolet and infrared spectra. Thus, in isooctane solution, the quinone methide VI has an intense band at 283 mμ (ϵ = 29,000). Also, it has bands at 6.15 and 6.07 μ ascribed to the conjugated carbonyl group,[11] and bands at 1.626, 2.079 and 2.140 μ, attributable to terminal methylene.[12] The ultraviolet spectra of several quinone methides are summarized in Table I, which shows that the effect of solvent or of substituents on the methylene group of the quinone methide changes the position of the intense, long wave length ultraviolet bands in the expected direction.

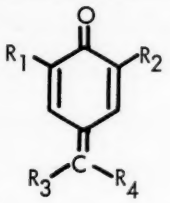
---

[11] G. M. Coppinger and J. W. Campbell, Ibid. 75, 734 (1953); M. S. Kharasch and B. S. Joshi, J. Org. Chem. 22, 1435 (1957).

[12] R. F. Goddu, Anal. Chem. 29, 1790 (1957).

1960

Table I Ultraviolet Spectra of Quinone Methides



R_1	R_2	R_3	R_4	Isooctane $\lambda_{max.}$	Isooctane Log ϵ	MeOH $\lambda_{max.}$
CH_3 [a,b]	CH_3	H	H	283	4.46	ca. 290
CH_3 [b]	CH_3	H	CH_3	297	4.40	ca. 312
CH_3 [b]	CH_3	H	CH_2=CH	329	4.62	338
t-Bu [b]	CH_3	H	H	285	4.35	290
t-Bu [a,c]	t-Bu	H	H	285	4.45	289
t-Bu [b,d]	t-Bu	H	CH_3	299	4.42	303
t-Bu [d]	t-Bu	CH_3	CH_3	314	4.40	322

[a-d] Prepared by: [a] Et_3N method; [b] Ag_2O method; [c] PbO_2 method; [d] Alkaline ferricyanide method[6]

The stability of the simple quinone methides in inert solvents appears to be a function of concentration. Thus, the quinone methide VI is stable for days at room temperature at a concentration of 10^{-5} M in inert solvents. As the concentration is increased, the disappearance of methide becomes more rapid, so that a 10^{-2} M solution was more than 60% reacted in 140 minutes at room temperature. The reaction products are primarily dimeric materials.[5] The 2,6-di-t-butyl analog of VI is more stable than VI at 10^{-2} M concentration in isooctane, only about 2% having reacted in 72 hours. Even here, we have so far been unsuccessful in attempts to isolate the pure material by evaporation of the solvent at reduced pressure. This procedure yields a mixture of products no longer having the spectrum of quinone methide. The only compound clearly

identified was 3,5,3',5'-tetra-t-butylstilbene-4,4'-quinone.[13] It is obvious that the stability of the quinone methides toward tail-to-tail dimerization is increased enormously by methyl groups on the terminal methylene. Thus, 2,6-di-t-butyl-4-ethenyl quinone methide,[6] with one such methyl group, is an easily isolable compound, and 2,6-di-t-butyl isopropenyl quinone methide[6] is stable for days at room temperature in the solid state.

The same dimeric products formed from quinone methides have also been formulated as arising from aryloxy radicals, either by rearrangement to benzyl radicals and dimerization of these[9] or by way of a complex between two of the aryloxy radicals which yield the final products.[14] Thus the present observation that quinone methides are converted to dimeric species has implications for the whole question of the mechanism of formation of dimeric materials during oxidation of phenols.

Toward lithium aluminum hydride, hydrogen chloride and various hydroxylic species, the quinone methide VI shows the expected behavior. Lithium aluminum hydride yields mesitol and the other species give rise to the appropriate benzyl derivative V from 1,6-addition. These reactions were demonstrated spectroscopically, the yields being essentially quantitative, and the products from reactions with methanol, acetic acid, and lithium aluminum hydride were isolated and found identical with authentic specimens. The chemical behavior of the quinone methide VI from oxidation of mesitol confirmed that it was essentially

---

[13] C. D. Cook, J. Org. Chem., 18, 261 (1953).

[14] J. K. Becconsall, S. Clough, and G. Scott, Proc. Chem. Soc., 308 (1959).

quantitatively the p-methide. No more than 2-3% of the ortho-isomer could have been present.

The high order of reactivity of the simple quinone methides is demonstrated by the rate of their reactions with methanol. The rate constant for reaction of the quinone methide VI in neutral methanol at 25°, followed spectrophotometrically at 290 mμ, is 4.0×10^{-2} sec.$^{-1}$, the half-life of VI being 17 seconds. Thus, the quinone methide VI reacts with methanol approximately 100 times as fast as spiro[2,5]octa-1,4-diene-3-one[8] (IV). As summarized in Table II, reactivity toward methanol is only slightly reduced by methyl substitution in the methylene group of the quinone methide. On the other hand, 2,6-t-butyl groups exert a profound rate-retarding effect.

TABLE II

Rate Constants for Reaction
of Quinone Methides in Methanol at 25.0°C.
(R_1, R_2, R_3, R_4 as in Table I)

R_1	R_2	R_3	R_4	k (sec.$^{-1}$)
CH_3	CH_3	H	H	4.0×10^{-2}
CH_3	CH_3	H	CH_3	3.1×10^{-2} (23°)
CH_3	t-Bu	H	H	3.8×10^{-3}
t-Bu	t-Bu	H	H	9.4×10^{-5}
t-Bu	t-Bu	H	CH_3	5.5×10^{-5}
t-Bu	t-Bu	CH_3	CH_3	2.5×10^{-5}

It is interesting that every instance we have examined of a nucleophilic substitution reaction of a p-hydroxybenzyl derivative V proceeds by way of the quinone methide VI as an intermediate. Examples

are the hydrolysis of the chloride Va or its reaction with sodium acetate in acetic acid to produce the benzyl acetate Vb. Even attempted basic saponification of the benzyl acetate Vb produced the quinone methide intermediate.

Tetrahedron Letters No. 25, pp. 17-20, 1960. Pergamon Press Ltd. Printed in Great Britain

THE UNIQUE TRANSANNULAR METHYLATION OF 2-AMINO-4-HYDROXYPTERIDINE

D.J. Brown and N.W. Jacobsen

Department of Medical Chemistry

The Australian National University, Canberra, Australia

(Received 24 October 1960)

AMINO- and hydroxy-pteridines have invariably methylated on a nuclear-nitrogen atom of the ring bearing the substituents. Thus 4-amino-[1], 4-methylamino-[1], 2,4-diamino-[2], 4-amino-2-hydroxy-[2], 2-hydroxy-[3], and 4-hydroxy-[3], pteridines all methylate entirely on $N_{(1)}$ with the exception of the last example which also gives an O- and $N_{(3)}$-methyl derivative. Moreover, 6-hydroxy-, 7-hydroxy-, and 6,7-dihydroxy-, pteridines give respectively 5-, 8-, and 5,8-di-, methylated derivatives[3].

On the other hand, 2-amino-4-hydroxypteridine (I), which is the fundamental nucleus of most known natural

---

[1] D.J. Brown and N.W. Jacobsen, J. chem. Soc. 1978 (1960).

[2] D.J. Brown and N.W. Jacobsen, unpublished work.

[3] A. Albert, D.J. Brown, and H.C.S. Wood, J. chem. Soc. 2066 (1956).

pteridines, is now shown to undergo transannular methylation yielding 2-amino-4,8-dihydro-8-methyl-4-oxopteridine (VI). This phenomenon may be of particular interest if suggestions of $N_{(8)}$-substitution in natural pteridines (as in riboflavine) prove well founded[4].

2-Amino-4-hydroxypteridine (I) and methanolic methyl iodide at 100° for 12 hours yield a single ruby-coloured hydroiodide, $C_7H_8IN_5O$. Since methylation on $N_{(5)}$ is precluded by valency, the base must have one of the five structures (II-VI). These have now all been unambiguously prepared.

4-Hydroxy-2-methylaminopteridine (II), dec. 374-378°, resulted from condensing glyoxal with 4,5-diamino-6-hydroxy-2-methylaminopyrimidine, made from 4-amino-6-hydroxy-2-methylaminopyrimidine[5] via its 5-nitro derivative. Compound (II) was also made from (V) in alkali by a now familiar type of rearrangement[6,7]. 2-Amino-4-methoxypteridine (III),

---

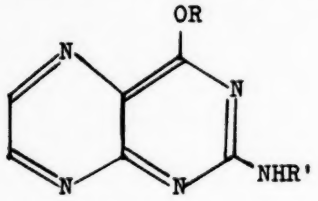
[4] Inter alia., H.S. Forrest and H.K. Mitchel, J. Amer. chem. Soc. 76, 5658 (1954); T. Masuda, T. Kishi, M. Asai, and S. Kuwada, Chem. pharm. Bull. 7, 366 (1959); R. Tschesche, F. Korte, and L. Reichle, Z. Naturforsch. 10B, 346 (1955); E.C. Taylor and H.M. Loux, J. Amer. chem. Soc. 81, 2474 (1959).

[5] B. Roth, J.M. Smith, and M.E. Hultquist, J. Amer. chem. Soc. 73, 2864 and 2869 (1951).

[6] D.J. Brown, E. Hoerger, and S.F. Mason, J. chem. Soc. 4035 (1955); D.J. Brown, Nature, in press.

[7] W.V. Curran and R.B. Angier, J. Amer. chem. Soc. 80, 6095 (1958).

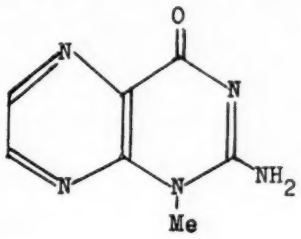
m.p. 204-205° (dec.), 2-amino-1,4-dihydro-1-methyl-4-oxopteridine (IV), m.p. 336° (dec.), and its 3,4-dihydro-3-methyl-isomer (V), dec. 319-320°, were made by similar condensations from respectively 2,4,5-triamino-6-methoxypyrimidine[5], 2,4,5-triamino-3,6-dihydro-3-methyl-6-oxopyrimidine[5,7], and its 1,6-dihydro-1-methyl-isomer[7].



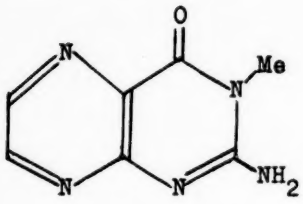
(I) R = R' = H

(II) R=H; R' = Me

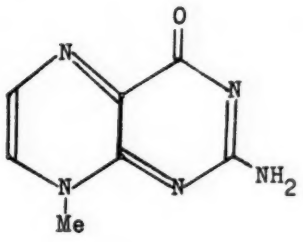
(III) R=Me; R' = H



(IV)



(V)



(VI)

In addition, mild alkaline hydrolysis of 2(4)-amino-1,4(1,2)-dihydro-4(2)-imino-1-methylpteridine[2] yielded (IV), and the position of methylation was confirmed by further degradation to 2-carboxy-3-methylaminopyrazine[2]. The remaining isomer (VI) was made from 2,5-diamino-4-hydroxy-6-methylaminopyrimidine[8] and glyoxal. The hydrochloride of

[8] W.E. Fidler and H.C.S. Wood, J. chem. Soc. 4157 (1957).

(VI) was identified with that of methylated-(I) by its decomposition point (280-285°; unchanged by admixture), by paper chromatography in six solvent systems, and by infrared spectrum.

We acknowledge the support of N.W.J. by a University Scholarship.

Tetrahedron Letters No. 25, pp. 21-25. 1960. Pergamon Press Ltd.
Printed in Great Britain

STERIC ENHANCEMENT OF RESONANCE

V. Baliah and (Miss) M. Uma

Department of Chemistry, Annamalai University,

Annamalainagar, India

(Received 10 October 1960)

THOUGH steric inhibition of resonance is well-known, steric enhancement of resonance is almost unknown. We report in this communication the electric dipole moments of a number of compounds which indicate that there is steric enhancement of resonance in some substituted anisoles and thioanisoles. The data given in Table 1 reveal certain interesting points.

Table 1

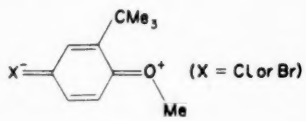
Anisole	μ(D) in C_6H_6 at 30°C	Reference Compound	μ(D)
2-t-Butyl-4-fluoro	2.16	p-F.C_6H_4.OMe	2.04[1]
2-t-Butyl-4-chloro	2.64	p-Cl.C_6H_4.OMe	2.32[2]
4-Bromo-2-t-butyl	2.74	p-Br.C_6H_4.OMe	2.23[3]
4-Chloro-2-methyl	2.58	p-Cl.C_6H_4.OMe	2.32
4-Bromo-2-methyl	2.52	p-Br.C_6H_4.OMe	2.23
4-Bromo-2,6-dimethyl	2.27	p-Br.C_6H_4.OMe	2.23

[1] N.J. Leonard and L.E. Sutton, J. Amer. Chem. Soc. 70, 1564 (1948).

[2] C.S. Copel and M.W. Rigg, ibid. 73, 3584 (1951).

[3] C.P. Smyth and W.S. Walls, ibid. 54, 3230 (1932).

In p-halogenoanisoles the dipole moment acts towards the halogen. So an alkyl group such as t-butyl or methyl, when present ortho to the methoxyl group, should be expected to cause a slight increase in the moment. This is indeed the case with 2-t-butyl-4-fluoroanisole. There is, however, a much higher increase in the moments of 2-t-butyl-4-chloro- and 4-bromo-2-t-butyl-anisole. The moment of 4-bromo-2-t-butylanisole is even greater than the sum of the moments of p-bromoanisole and t-butylbenzene. 4-Chloro- and 4-bromo-2-methylanisole also have significantly higher moments than those of p-chloro- and p-bromo-anisole, respectively, though the differences for the t-butyl compounds are larger. It is also of interest to note that the moment of 4-bromo-2,6-dimethylanisole is almost the same as that of p-bromoanisole. The larger moments of 2-t-butyl-4-chloro- and 4-bromo-2-t-butyl-anisole seem to be due to the O-methyl occupying a position away from the alkyl group. Such a preferred orientation will restrict the rotation of -OMe and the probability of its attaining planarity with the benzene ring will increase. Then the following structure, in which the halogen expands its valence shell by utilising



one of its vacant d-orbitals, makes a greater contribution

to the ground state of the molecule. When the halogen involved is fluorine, there can be no d-orbital resonance.[4]

If the above reasoning is correct, the dipole moments of 2-methyl-4-nitroanisole, 4-methoxy-3-methylacetophenone and methyl 2-methyl-4-nitrophenyl sulphide should also have moments higher than those expected. Furthermore, the dipole moments of 2,6-dimethyl-4-nitroanisole, 4-methoxy-3,5-dimethylacetophenone and methyl 2,6-dimethyl-4-nitrophenyl sulphide should almost be the same as or even lower than the moments of p-nitroanisole, p-methoxyacetophenone and methyl p-nitrophenyl sulphide, respectively, because in the former compounds there can be no preferred orientation of -OMe or -SMe to cause enhanced resonance. On the other hand the two ortho methyl groups will cause steric inhibition of resonance. With a view to testing these ideas the dipole moments of compounds listed in Table 2 have been experimentally determined and they have also been calculated for comparison.

The dipole moments of 2-methyl-4-nitroanisole, 4-methoxy-3-methylacetophenone and methyl 2-methyl-4-nitrophenyl sulphide are seen to support the concept of steric enhancement of resonance. The difference between the observed and

---

[4] V. Baliah and (Miss) M. Uma, Naturwiss. 45, 512 (1958).

Table 2

Compound	Dipole moment (D)	
	Observed (in C_6H_6 at 30°C)	Calcd. for free rotation of -OMe or -SMe
p-Nitroanisole	4.74	4.51
2-Methyl-4-nitroanisole	5.29	4.71
2,6-Dimethyl-4-nitroanisole	4.77	4.89
p-Methoxyacetophenone	3.51	3.37
4-Methoxy-3-methylacetophenone	3.91	—
4-Methoxy-3,5-dimethylacetophenone	3.49	3.62
Methyl p-nitrophenyl sulphide	4.36[5]	3.78
Methyl 2-methyl-4-nitrophenyl sulphide	4.77	3.99
Methyl 2,6-dimethyl-4-nitrophenyl sulphide	4.12	4.17

calculated moments of p-nitroanisole is 0.23 D which is attributable to the resonance interaction of the -OMe and $-NO_2$ groups. But in the case of 2-methyl-4-nitroanisole the difference between the observed and calculated moments is 0.58 D, the observed value being higher. This can only be interpreted to mean that the resonance interaction of

[5] H. Lumbroso and G. Dumas, Bull. soc. chim. France 651 (1955).

1960

-OMe and -NO_2 in this compound is greater than in p-nitroanisole. The same may be said of 4-methoxy-3-methylacetophenone and methyl 2-methyl-4-nitrophenyl sulphide. The view that there is steric enhancement of resonance in the above compounds gains further support from the fact that the expected steric inhibition of resonance is revealed in 4-substituted 2,6-dimethylanisoles.

Tetrahedron Letters No. 25, pp. 26-31, 1960. Pergamon Press Ltd.
Printed in Great Britain

FURTHER EXAMPLES OF BIOLOGICAL C-METHYLATION: NOVOBIOCIN AND ACTINOMYCIN

A.J.Birch, D.W.Cameron, P.W.Holloway
and R.W.Rickards
Department of Chemistry,
The University, Manchester

(Received 19 October 1960)

AMONG major biological pathways leading to compounds carrying C-methyl groups are those involving terpenoid intermediates (e.g. mevalonic acid[1]), branched chain amino-acids (e.g., valine, leucine, isoleucine[2]), propionic acid (or methylmalonyl-coenzyme-A[3,4]), or transmethylation from C_1-donor systems (e.g., methionine,

---

[1] cf. J.W.Cornforth, J.Lipid Res. 1, 3 (1959).

[2] cf. W.E.Knox and E.J.Behrman, Ann.Rev.Biochem. 28, 223 (1959).

[3] A.J.Birch, E.Pride, R.W.Rickards, P.J.Thomson, J.D.Dutcher, D.Perlman and C.Djerassi, Chem.and Ind. 1245 (1960).

[4] J.W.Corcoran, T.Kaneda and J.C.Butte, J.Biol.Chem. 235, PC29 (1960); H.Grisebach, H.Achenbach and U.C.Grisebach, Naturwiss. 47, 206 (1960); Z.Vanek, personal communication.

1960

choline, betaine). This last process has been shown to be responsible for "introduced"methyl substituents in acetate-derived aliphatic[5,6] and phenolic[7] structures, terpenoids,[8] branched chain monosaccharides,[9] and the porphyrin-like moiety of vitamin B_{12}.[10] We now wish to report the occurrence of a further type of biological transmethylation.

Fermentation of Streptomyces niveus in the presence of L-[$^{14}CH_3$]methionine yielded novobiocin[11] (I, * denotes ^{14}C) (with 10% isotope incorporation) in which the

---

5 A.J.Birch, P.Fitton, E.Pride, A.J.Ryan, H.Smith and W.B.Whalley, J.Chem.Soc. 4576 (1958).

6 A.J.Birch, J.F.Snell and P.J.Thomson, J.Amer.Chem.Soc. 82, 2402 (1960).

7 A.J.Birch, R.J.English, R.A.Massy-Westropp, M.Slaytor and H.Smith, J.Chem.Soc. 365 (1958)

8 G.J.Alexander and E.Schwenk, J.Amer.Chem.Soc. 79, 4554 (1957).

9 Z.Vanek, personal communication.

10 R.Bray and D.Shemin, Biochim.Biophys.Acta 30, 647 (1958).

11 J.W.Hinman, E.L.Caron and H.Hoeksema, J.Amer.Chem.Soc. 78, 2019 (1956); idem, ibid. 79, 3789 (1957); C.H.Shunk, C.H.Stammer, E.A.Kaczka, E.Walton, C.F.Spencer, A.N.Wilson, J.W.Richter, F.W.Holly and K.Folkers, ibid. 78, 1770 (1956).

radioactivity was distributed specifically between the C-methyl of the coumarin system (35%), the O-methyl of the noviose moiety (35%), and the gem-dimethyl group of the latter (31%, probably one methyl only being introduced). The same methyl cation donor was utilised (to the extent of 15%) in the biosynthesis of actinomycin (a typical structure[12] II) by an unidentified Streptomyces species, providing specifically the two nuclear C-methyl groups (28% of the total antibiotic radioactivity), in addition to portion, presumably the N-methyl groups, of the peptide chains.

These results provide the first unequivocal demonstration of methyl transfer from methionine (probably as the S-adenosyl derivative[13]) to carbon in an aromatic ring system derived by the shikimic acid route,[14] since it has been shown[15] that the coumarin moiety of novobiocin (I) arises from tyrosine.

---

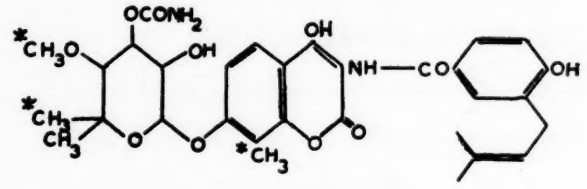
[12] H.Brockmann, Fortschr.Chem.org.Naturstoffe, Springer, Vienna, 18, 1 (1960).

[13] L.W.Parks, J.Amer.Chem.Soc. 80, 2023 (1958).

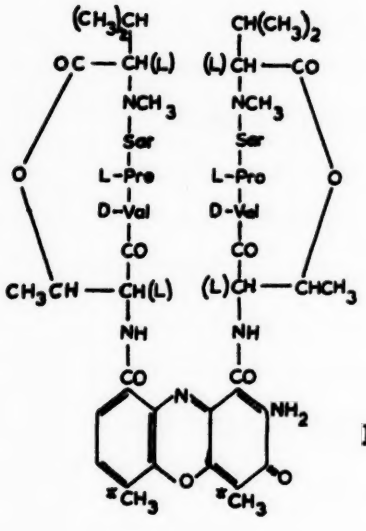
[14] B.D.Davis, Arch.Biochem.Biophys. 78, 497 (1958), and references there cited.

[15] K.Chambers, G.W.Kenner, M.J.T.Robinson and B.R.Webster, Proc.Chem.Soc. 291 (1960).

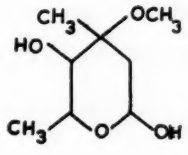
It is also likely, but not proven, that the nucleus of the actinomycins (e.g. II) is formed by oxidative dimerisation of appropriate hydroxy-anthraniloyl units (cf. ref.[16]) arising from shikimic acid.



I



II



III

---

[16] H.Brockmann and H.Lackner, Naturwiss. 47, 230 (1960).

It is notable that the three "introduced" methyl substituents of novobiocin carry approximately the same radioactivity (cf. terramycin[6] and mycophenolic acid[7]). We have not identified the variable peptide chains (cf. ref.[12]) present in the actinomycin preparation, but assuming the presence of four N-methyl groups in terminal N-methyl valine and sarcosine units (as in the commonest natural actinomycins[12]), then the extent of isotope utilisation for nuclear C-methylation is comparable to, although slightly lower than, that for N-methylation. The derivation from methionine of a C-methyl group of noviose is in accord with similar results[9] for the related cladinose (III) of erythromycin, and indicates formation of such branched chain monosaccharides by methylation of a pre-existing skeleton, as opposed to elaboration by aldol- or ketol-type condensations of small units[17] or by processes similar to those of fatty acid biosynthesis.[18]

The production by mutation of Streptomyces strains

---

17 L.Hough and J.K.N.Jones, Nature 167, 180 (1951).

18 R.B.Woodward, Festschrift Arthur Stoll, Birkhauser, Basle, p.524 (1957).

1960

capable of producing demethyltetracyclines[19] by omission of the biological C-methylation stage,[6] indicates that such demethyl antibiotics could probably be obtained by similar mutations in the organisms producing novobiocin or actinomycin.

We are indebted to Dr.M.Lumb and Dr.P.E.Macey, Boots Pure Drug Co.Ltd., Nottingham, for their generous co-operation with fermentations of Streptomyces niveus, and for providing the actinomycin-producing culture and samples of actinomycin. Novobiocin was kindly supplied by the Upjohn Co., Kalamazoo. We thank the Royal Commission for the Exhibition of 1851 for a Scholarship (D.W.C.), the D.S.I.R. for a Research Grant (P.W.H.) and the Rockefeller Foundation for financial support.

---

[19] J.R.D.McCormick, N.O.Sjolander, U.Hirsch, E.R.Jensen and A.P.Doerschuk, J.Amer.Chem.Soc. 79, 4561 (1957).

Tetrahedron Letters No. 25, pp. 32-36, 1960. Pergamon Press Ltd. Printed in Great Britain

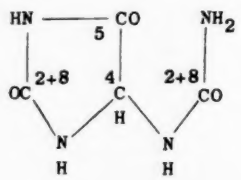
UREIDE BIOSYNTHESIS IN HIGHER PLANTS

H. Reinbothe and K. Mothes

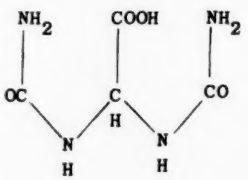
Institut für Allgemeine Botanik der Universität Halle/S., and Institut für Biochemie der Pflanzen der Deutschen Akademie der Wissenschaften in Halle/S.

(Received 9 November 1960)

THE origin and fate of allantoin and allantoic acid in plant tissue is at present not quite clear.



allantoin



allantoic acid

As a result of the work of Fosse et al[1] and of Mothes and Engelbrecht[2] we know that these glyoxylic acid ureides are major constituents of members of some plant families. The ureides play an important role in the nitrogen economy of such plants. Thus allantoin and allantoic acid function for the storage and translocation of nitrogen[2,3].

In the animal kingdom allantoin arises from oxidative purine

---

1 Listed by Bollard, E.G., Symp. Soc. exp. Biol. 13, 304 (1959).

2 K. Mothes, Encyclopedia of Plant Physiology, Vol. VIII, p. 716, Heidelberg, (1958).

3 K. Mothes and L. Engelbrecht, Flora 139, 586 (1952); 141, 356 (1954)

1960

degradations. In the course of the hydrolysis of nucleoprotein, ureides are formed as intermediates of the catabolic sequence of reactions. In plants, however, the high level of nitrogen stored as allantoin and allantoic acid cannot be derived from nucleic acid breakdown alone. Ureide accumulation is related to protein metabolism. Allantoin and allantoic acid appear as special products of ammonia detoxication in some plants.

Certain indications of the metabolic role and origin of ureides in wheat emerge from the results of Krupka and Towers[4]. Glycine is a more immediate precursor for allantoin biosynthesis than glyoxylic acid which presumably enters ureide formation via glycine. The result of feeding experiments with xanthine and uric acid are consistent with the view that the biogenesis of allantoin involves purine synthesis and breakdown. Barnes[5] demonstrated with the aid of adenine-8-C^{14} that the breakdown of purines in leaves of Acer saccharinum is concerned in ureide biosynthesis. There is some evidence that ureides can also be formed directly from simpler molecules. When extracts of certain higher fungi were incubated with a mixture of glyoxylate and urea, glyoxylic acid disappeared and allantoic acid was formed[6]. But it is as yet questionable whether allantoin can be derived from allantoic acid by dehydration.

Material and Methods.

Ureide biosynthesis was studied in plants which have a high content of allantoin or allantoic acid. "Allantoin plants" like Boraginaceae contain only traces of allantoic acid. "Allantoic acid plants", e.g. Acer negundo contain allantoic acid as the predominant glyoxylic acid

---

4 R. M. Krupka and G. H. N. Towers, Canad. J. Bot. 36, 165, 179 (1958); 37, 539 (1959).

5 R. L. Barnes, Nature 184, 1944 (1959).

6 M. A. Brunel and G. Brunel-Capelle, C. R. Acad. Sci. 232, 1130 (1951).

ureide. But allantoin can also be present in even greater amounts and in such plants free urea is found. Different C^{14}-labelled compounds were fed alone or in combination with hypothetical precursors or inhibitors of ureide synthesis. Plant material was extracted twice with hot 70% alcohol and the extracts submitted to paper chromatographic analysis directly or after fractionation on columns of Dowex 50 (H^+). Propanol-water (aceotr.) and phenol-water (3:1, g/v) were used as solvent systems for the two-dimensional separation of amino acids and ureides. Autoradiographs were prepared using Agfa-Duro-safety-X-ray film. Amino acids were detected with ninhydrin reagent, urea and urea derivatives with Ehrlich's reagent. Allantoin and allantoic acid were estimated as glyoxylic acid by colorimetry in an Eppendorf-photometer at 546 m [7]. Radioactive measurements were made by means of a thin end-window Geiger-Müller tube. Specific activities and incorporation rates were determined after isolation of allantoin-C^{14} by a combined procedure of column chromatography and double repeated one-dimensional paper chromatography. Radioactivity of allantoin-C^{14} was measured on alumina discs in infinite sample thickness. The respective quantity was estimated in an aliquot part. The position of C^{14} in allantoin was cleared up after hydrolysis to glyoxylic acid and urea which were separated from each other by column chromatography on Dowex 1 (formate). The specific activities of allantoin and urea released by hydrolysis were determined. From these data the distribution of radioactivity over the sum of carbon atoms 4 and 5, also 2 and 8 was calculated.

Allantoin Plants.

Glycine-1-C^{14}, glycine-2-C^{14} and glyoxylic acid-1,2-C^{14} were fed to

---

[7] G. E. Young and C. F. Convay, J. Biol. Chem. 142, 839 (1942).

1960

detached leaves of Platanus orientalis, Cynoglossum officinale and Symphytum officinale, seedlings of Borago officinalis, and storage roots (root sections) of comfrey. In each case radioactivity was mainly incorporated into serine and allantoin. Glyoxylic acid gives rise to the formation of glycine and serine. Presumably glyoxylate participates in allantoin synthesis via glycine. Glycine and serine are interconvertible in roots of Symphytum. Glycine carbon enters allantoin in position 4 and 5. The methylene grouping also forms carbon atoms 2 and 8 presumably via binding to tetrahydrofolic acid derivatives. Serine synthesis is understood as a C-1-transfer to glycine as acceptor. Folic acid ($1{,}6 \times 10^{-6}$ m) stimulated allantoin formation from glycine. Sulphonamides as e.g. sulphanilamide (10^{-3} m), sulphathiazole (10^{-3} m), and sulphadiazine (10^{-4} m) had little or no effect upon allantoin synthesis from glycine. Added purines as e.g. adenine, hypoxanthine, xanthine, and uric acid were effective in decreasing allantoin-C^{14} production from labelled glycine in an order which is in accordance with their relative positions in aerobic purine breakdown. Purine antagonists as e.g. 8-azaxanthine and benzimidazole stimulated allantoin formation from glycine slightly. Possibly these purine analogues inhibit the incorporation of purines formed by the de novo purine synthesis into nucleic acids in a competitive manner. Thus purines will be transformed more rapidly to allantoin by degradation. Urea-C^{14} alone or in combination with glyoxylic, mesoxalic or tartronic acids was not transferred either to allantoin or to allantoic acid. Urea is broken down to ammonia and carbon dioxide. Ammonia raises the level of glutamine, carbon dioxide is incorporated into different nitrogen compounds by carboxylations. In the presence of inactive glycine or glyoxylate $C^{14}O_2$ is very readily incorporated into glycine, serine and

allantoin by an unknown fixation mechanism. This effect is still under investigation.

Allantoic Acid Plants.

In plants such as Acer negundo, Aesculus hippocastanum and Pelargonium zonale glycine-C^{14} is predominantly incorporated into serine, allantoic acid and allantoin. In chlorophyll-deficient leaves of these plants the methylene-C-atom of glycine enters urea formation via the ureide groupings of allantoin and allantoic acid. Added purines and allantoin are decomposed to allantoic acid, glyoxylic acid and urea in white leaves of Acer negundo. The first products of glyoxylate metabolism in chlorophyll-deficient leaves of Pelargonium zonale were glycine and serine. Urea is broken down by the action of urease to ammonia and carbon dioxide in allantoic acid plants. Urease activity could be inhibited in the presence of alloxanic acid[8] or mesoxalic acid. But urea is also transferred as a molecule to allantoic acid (urease activity is not very effective). In the presence of glyoxylic acid the production of allantoic acid from urea was stimulated; allantoin was also formed to a small extent. But glyoxylic acid and urea react already spontaneously at quite low concentration to form allantoic acid at room temperatures. Spontaneous allantoin formation involving urea and glyoxylate is achieved only under more extreme conditions and even then only to a small extent. If the reaction partners are available a resynthesis of ureides appears to be possible. Further studies are needed in order to clear up the mechanism and physiological role of such reaction paths in allantoic acid plants.*

* A more detailed account and discussion of the results will be published in Flora (Jena).

[8] C. T. Gray, M. S. Brooke and J. C. Gerhart, Nature 184, 1936 (1959).

Tetrahedron Letters No. 25, pp. 37-43, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

THE SYNTHESIS OF dl-SANDARACOPIMARADIENE, dl-PIMARADIENE AND SOME OBSERVATIONS ON THE STRUCTURE OF RIMUENE[1]

Robert E. Ireland and Peter W. Schiess

Department of Chemistry, The University of Michigan

Ann Arbor, Michigan

(Received October 20, 1960)

In the field of total synthesis of the diterpenoid resin acids, efforts reported to date have concerned themselves with construction of the appropriate A and B rings[2]. We now wish to report the results of a program directed toward the elaboration of the ring C substitution pattern present in the pimaric acids.

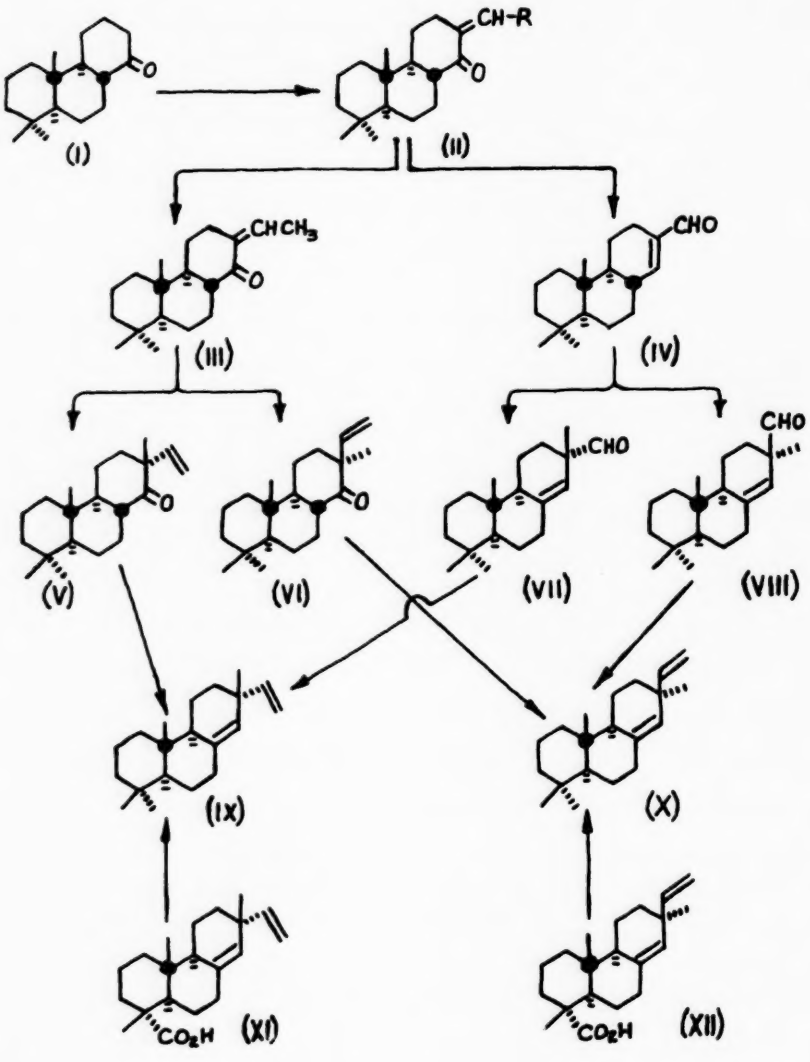
When the tricyclic ketone(I), prepared independently in substantially the same fashion as that reported by Turner and co-workers[3], was condensed with ethyl formate in the presence of sodium methoxide and then with pyrrolidine, there resulted an 83% yield of the pyrrolidinomethylene ketone(II, R=C_4H_8N)

---

[1] A portion of this work was presented at the International Symposium on The Chemistry of Natural Products, Sydney, Australia, August, 1960.

[2] For example, see G. Stork and J. W. Schulenberg, J. Am. Chem. Soc. 78, 250 (1956); E. Wenkert and A. Tahara, J. Am. Chem. Soc. 82, 3229 (1960); J. A. Barltrop and A. C. Day, Chemistry and Industry 1450 (1959); V. R. Ghatak, D. K. Datta and S. C. Ray, J. Am. Chem. Soc. 82, 1728 (1960).

[3] R. B. Turner and P. E. Shaw, Tetrahedron Letters No. 18, 24 (1960).


CH-R
O
(I)
(II)
CHCH3
CHO
(III)
(IV)
CHO
CHO
(V)
(VI)
(VII)
(VIII)
(IX)
(X)
CO2H
CO2H
(XI)
(XII)

1960

m.p. 154-156° (C,80.17%; H,10.65%; N,4.20%). Treatment of this derivative with methyl magnesium bromide[4] and then 2N aqueous hydrochloric acid afforded a 90% yield of the corresponding ethylidene ketone(III) m.p. 76-76.5°(λ_{max}^{alc} 292 mμ(7070); C,82.99%; H,10.96%).

Completion of the substitution at C13[5] was accomplished by methylation of the ethylidene ketone(III) with methyl iodide in the presence of potassium t-butoxide in t-butyl alcohol. Chromatography of the resulting mixture of C13 epimers on Florisil afforded first a 5% yield of the ketone(VI) m.p. 78-80°(C,83.33%; H,11.18%) and then a 30% yield of its epimer (V) m.p. 69-70°(C,83.14%; H,11.08%). The assignment of this stereochemistry to these ketones is based on their chromatographic behaviour and their ultraviolet spectra. On both column and gas-liquid chromatography, the higher melting ketone is eluted first, a result expected of the compound containing an axially oriented vinyl group. The homoconjugation[6] expected of the axially oriented α-vinyl ketone is observed in the ultraviolet spectrum of the higher melting ketone -λ_{max}^{alc} 294mμ(104)- and the lack of significant conjugation between the vinyl grouping and the carbonyl in the lower melting

---

[4] C. Jutz, Ber. 91, 1867 (1958).

[5] Steroid numbering is used throughout, and although formulas of only one enantiomer are drawn, they are taken to represent a racemate except were indicated.

[6] R. C. Cookson and N. S. Wariyar, J. Chem. Soc. 2302 (1956); H. Labhart and G. Wagniere, Helv. Chim. Acta 42, 2219 (1959).

ketone -λ_{max}^{alc} 292mμ(50)- attests to the equatorial conformation of its vinyl grouping.

The final stages of the synthesis were accomplished by reducing each ketone with sodium in alcohol, followed by benzoylation and pyrolytic elimination of benzoic acid. Thus the higher melting ketone(VI) led to the diene(X)(C,88.26%; H,11.84%; 90% homogeneous by gas-liquid chromatography) as an oil through the corresponding 14β-benzoate, m.p. 82-84°(C, 82.15%; H,9.81%) in 61% yield. Similarly the lower melting ketone(V) was converted to the diene(IX)(C,88.21%; H,11.81%; 95% homogeneous by gas-liquid chromatography) also an oil *via* its 14β-benzoate, m.p. 125-126°(C,82.01%; H,9.76%) in 70% yield.

Despite the success attained in the above synthesis, the final pyrolytic decomposition was considered a weak point in the synthetic scheme. In order to circumvent this step the ketone(I) was converted in 72% yield to the cyclohexyl enol ether (II,R=$C_6H_{11}O$) m.p. 119-120°(C,80.21%; H,10.80%) by etherification[7] of the above mentioned hydroxymethylene derivative with cyclohexanol. Reduction[8] with sodium borohydride in methanol and subsequent treatment with aqueous mineral acid afforded the aldehyde(IV) m.p. 81-83°(C,83.18%; H,10.83%) in 66% yield. This aldehyde was readily methylated with methyl iodide in the presence of potassium t-butoxide in t-butyl alcohol. When the resulting mixture of epimeric βγ-unsaturated

---

[7] A. Eschenmoser, J. Schreiber and S. A. Julia, Helv. Chim. Acta 36, 482 (1953).

[8] P. Seifert and H. Schinz, Helv. Chim. Acta 34, 728 (1951).

aldehydes was separated by chromatography on Florisil, there was obtained first a 25% yield of the axial aldehyde(VIII) m.p. 58-60°(C,83.30%; H,11.15%) and then a 35% yield of the equatorial aldehyde(VII) m.p. 77-80°(C,83.22%; H,11.02%). Each aldehyde was shown to be homogeneous by gas-liquid chromatography and stereochemical assignment was tentatively made on the basis of their chromatographic behaviour. This assignment was confirmed by the conversion of each aldehyde into the corresponding diene by treatment with methylenetriphenylphosphorane[9] in ether solution. Thus the axial aldehyde(VIII) afforded the diene(X), m.p. 28-31°(C,88.00%; H,11.75%; homogeneous on gas-liquid chromatography) in 83% yield, and the equatorial aldehyde(VII) afforded the diene(IX) m.p. 22-25°(C,88.21%; H,11.78%; homogeneous on gas-liquid chromatography) in 85% yield. The infrared spectra and the retention times on gas-liquid chromatography of the dienes prepared by the latter synthesis are identical to those obtained via the first route. This latter synthesis proves beyond doubt that no rearrangement had occurred during the pyrolytic elimination employed in the first approach and furthermore represents a more convenient and effective method for construction of the pimaric acid ring C substitution pattern.

Since we have been able to synthesize the dl-dienes(IX) and (X) of known stereochemistry, especially about C13, it

---

[9] G. Wittig and V. Schöllkopf, Ber. 87, 1318 (1954).

became of interest to corroborate independently the stereochemical assignment[10] of the resin acids - particularly, sandaracopimaric(XI) and pimaric(XII). Each acid was converted by standard methods[11] to its corresponding diene: sandaracopimaric acid(XI) afforded sandaracopimaradiene(IX), m.p. 41-42°, $[\alpha]_D$-12° (C,87.97%; H,11.68%) in 56% overall yield, and pimaric acid(XII) yielded pimaradiene(X) m.p. 24-26°, $[\alpha]_D$+99° (C,87.97%; H,11.83%) in 66% yield. The infrared spectrum of *l*-sandaracopimaradiene is identical to the dl-diene(IX), thus substantiating the quasi-equatorial nature of the vinyl group in sandaracopimaric acid(XI). The infrared spectrum of *l*-pimaradiene is identical to the dl-diene(X), thereby corroborating the quasi-axial conformation of the vinyl group in pimaric acid(XII). Further substantiation of the identity of the active dienes and their dl-counterparts is found in gas-liquid chromatography where *l*-sandaracopimaradiene has an identical retention time to that of the dl-diene(IX) and d-pimaradiene to that of the dl-diene(X).

---

10 E. Wenkert and J. W. Chamberlin, J. Am. Chem. Soc. 80, 2912 (1958); 81, 688 (1959); B. Green, A. Harris and W. B. Whalley, J. Chem. Soc. 4715 (1958); O. E. Edwards and R. Howe, Can. J. Chem. 37, 760 (1959); Chemistry and Industry 537 (1959); H. R. Bruun, Acta Chem. Scand. 13, 379 (1959); and J. C. W. Chien, J. Am. Chem. Soc. 82, 4762 (1960).

11 These conversions were made by the sequence: $R\text{-}CO_2H \rightarrow R\text{-}CH_2OH \rightarrow R\text{-}CHO \rightarrow R\text{-}CH{=}NNHCONH_2 \rightarrow R\text{-}CH_3$. Although space does not permit further elaboration, each stage went in high yield and all intermediate products were characterized by infrared spectra and combustion analysis.

The structure represented here for sandaracopimaradiene(IX) has been proposed[12] for the hydrocarbon rimuene. A direct comparison of our synthetic diene(IX) - both active and dl - with a sample of rimuene has shown the two to be different, and we are therefore forced to the conclusion that the structure of rimuene is incorrect. The recently reported conversion of sandaracopimaric acid to rimuene in unstated yield by Petru and co-workers[13] suffers from the use of a Raney nickel desulfurization at the final stage which could have isomerized the diene system. This point is under further scrutiny in these laboratories.

Acknowledgements: We gratefully acknowledge the support of this investigation by a research grant (G-5912) from The National Science Foundation. We express our thanks to Dr. O. E. Edwards for making available generous samples of the resin acids used in this work and to Professor L. H. Briggs for his cooperation and the sample of rimuene. We are indebted to Professor W. E. M. Lands of the Biochemistry Department for assistance with the gas-liquid chromatography and to the Parke, Davis and Co. Spectral Laboratory for the infrared analyses referred to in this work. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Michigan.

---

[12] L. H. Briggs, B. F. Cain, B. R. Davis and J. K. Wilmhurst, Tetrahedron Letters No. 8, 13 (1959).

[13] V. Galik, J. Kuthan and F. Petru, Chemistry and Industry 722 (1960).

Tetrahedron Letters No. 25, pp. 44-47, 1960. Pergamon Press Ltd. Printed in Great Britain

LABORATORY REALIZATION OF THE SCHÖPF-OECHLER SCHEME OF VASICINE SYNTHESIS[1,2]

Nelson J. Leonard and Michael J. Martell, Jr.

The Noyes Chemical Laboratory, University of Illinois, Urbana, Illinois

(Received 4 November 1960)

ALTHOUGH syntheses of the alkaloid vasicine (peganine) (IV) have been reported,[3,4,5] the original facile scheme (I + II ⟶ III ⟶ IV) proposed by Schöpf and Oechler,[6] based on implied biogenesis, has remained untested due to the unavailability of the requisite precursor, γ-amino-α-hydroxybutyraldehyde (II). We now wish to report the synthesis of the long-sought II (as its diethyl acetal), which we required also in model syntheses of hydroxylated pyrrolizidines,[7] and its ready conversion to dl-vasicine (IV) under mild conditions.

---

[1] This investigation was supported by a research grant (USPHS-RG 5829) from the National Institutes of Health, Public Health Service.

[2] Presented in part at the International Symposium on the Chemistry of Natural Products, International Union of Pure and Applied Chemistry, Australia, August, 1960.

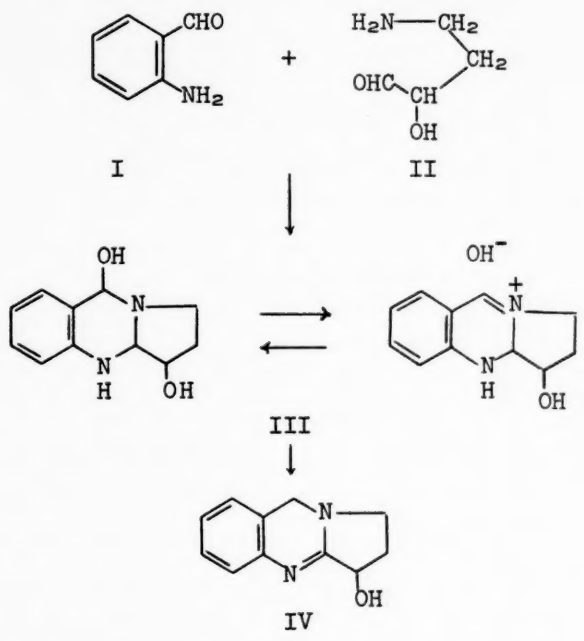
[3] E. Späth, F. Kuffner and N. Platzer, Ber. 68, 699 (1935).

[4] E. Späth and N. Platzer, ibid. 69, 255 (1936).

[5] P. L. Southwick and J. Casanova, Jr., J. Am. Chem. Soc. 80, 1168 (1958).

[6] C. Schöpf and E. Oechler, Ann. 523, 1 (1936).

[7] N. J. Leonard and S. W. Blum, J. Am. Chem. Soc. 82, 503 (1960).



β-Cyanolactaldehyde diethyl acetal, b.p. 87-88° /0.5 mm., n_D^{25} 1.4344 (Found: C, 55.39; H, 8.85; N, 8.02. $C_8H_{15}NO_3$ requires: C, 55.47; H, 8.73; N, 8.09%), was formed from acrolein diethyl acetal chlorohydrin,[8,9] or more conveniently from glycidaldehyde diethyl acetal[10] (70%) with potassium cyanide in aqueous ethanol. That epoxide ring opening had occurred in the desired manner[11]

---

[8] A. Wohl, Ber. 31, 1796 (1898).

[9] D. I. Weisblat, B. J. Magerlein, D. R. Myers, A. R. Hanze, E. I. Fairburn and S. T. Rolfson, J. Am. Chem. Soc. 75, 5893 (1953).

[10] We are grateful to the Shell Development Company, Emeryville, California, for a generous sample of glycidaldehyde and directions for its conversion to the diethyl acetal.

[11] R. E. Parker and N. S. Isaacs, Chem. Revs. 59, 737 (1959).

was established by forming the tosylate of the cyanohydroxy-acetal with p-toluenesulfonyl chloride in pyridine and then reducing the crude tosylate with lithium aluminum hydride in tetrahydrofuran. Distillation of the residue afforded pure γ-aminobutyraldehyde diethyl acetal,[12] b.p. 84-85° /ca. 12 mm., n_D^{25} 1.4260 (34% over-all) (Found: C, 59.33; H, 11.87; N, 8.51. $C_8H_{19}NO_2$ requires: C, 59.59; H, 11.88; N, 8.69%), which was converted (85%) to γ-2,4-dinitrophenylaminobutyraldehyde diethyl acetal, m.p. 53.5-54.5° (Found: C, 51.65; H, 6.59; N, 12.66. $C_{14}H_{21}N_3O_6$ requires: C, 51.37; H, 6.47; N, 12.84%), identical with the derivative obtained by reaction of 2,4-dinitrofluorobenzene (DNFB) with authentic γ-aminobutyraldehyde in water at 40°. Reduction of the β-cyanolactaldehyde diethyl acetal in ether with lithium aluminum hydride proceeded smoothly to give the diethyl acetal of γ-amino-α-hydroxybutyraldehyde (II) (63%), b.p. 77-78° /0.4 mm., n_D^{25} 1.4479 (Found: C, 54.22; H, 10.68; N, 7.74. $C_8H_{19}NO_3$ requires: C, 54.21; H, 10.81; N, 7.90%); N-2,4-dinitrophenyl derivative, m.p. 76-77° (Found: C, 48.95; H, 6.18; N, 11.94. $C_{14}H_{21}N_3O_7$ requires: C, 48.97; H, 6.17; N, 12.24%).

With γ-amino-α-hydroxybutyraldehyde diethyl acetal in hand, the synthesis of vasicine was readily accomplished, parallel to the path leading to desoxyvasicine.[6,13,14] Liberation of II from the diethyl acetal in dilute aqueous solution at pH

---

[12] R. H. F. Manske, Can. J. Research 5, 592 (1931).

[13] L. Macholán, Collection Czech. Chem. Communs. 24, 550 (1959).

[14] L. Skursky, Z. Naturforsch. 14B, 474 (1959).

1960

2.5 at 85° during 35 minutes followed by reaction with o-aminobenzaldehyde at pH 5.5 (aqueous phosphate buffer) for 3 days at room temperature gave an orange solution, which was then stirred vigorously with palladium-on-barium-sulfate catalyst under a stream of hydrogen at 60° for 1.5 hours. Basification and continuous ether extraction yielded (39% overall) dl-vasicine, m.p. 211-211.5° (slight dec., evac. cap.) after recrystallization and sublimation at 160° /0.05 mm. (Found: C, 70.33; H, 6.32; N, 14.80. $C_{11}H_{12}N_2O$ requires: C, 70.18; H, 6.43; N, 14.88%). This product was in every way identical with a sample of racemized[15] l-vasicine.[16] Since dl-vasicine has been resolved,[15] the synthesis will also provide the active forms. It may also be pointed out that the simple combination of γ-amino-α-hydroxybutyraldehyde with substituted o-aminobenzaldehydes could lead to a variety of substituted vasicines.

Acknowledgement--The authors wish to thank Dr. S. W. Blum, University of Minnesota, for his very helpful suggestions.

---

[15] E. Späth, F. Kuffner and N. Platzer, Ber. 68, 1384 (1935).

[16] We are grateful to Prof. Roger Adams for a sample of l-vasicine.

1960

Tetrahedron Letters No. 26, pp. 1-4, 1960. Pergamon Press Ltd. Printed in Great Britain

THE STRUCTURE OF DIHYDROTOXIFERINE

V. Boekelheide, O. Ceder, T. Crabb, Y. Kawazoe and R. N. Knowles

Department of Chemistry, University of Rochester

Rochester, New York

(Received 9 November 1960)

THE dimerization of Wieland-Gumlich aldehyde or its methochloride represents an extremely simple synthesis for nor-C-toxiferine-I or C-toxiferine-I, respectively,[1-5] and provided a brilliant break-through in the structural investigation of the principal alkaloids of calabash-curare.[6] Although this discovery combined with the conversion of Wieland-Gumlich aldehyde to C-dihydrotoxiferine[1,2] clearly establishes the carbon skeletons of C-dihydrotoxiferine and C-toxiferine-I, two possibilities still remain for the arrangement of the double bonds in the central portion of the molecule.

---

[1] K. Bernauer, F. Berlage, W. von Philipsborn, H. Schmid and P. Karrer, Helv. Chim. Acta 41, 2293 (1958).

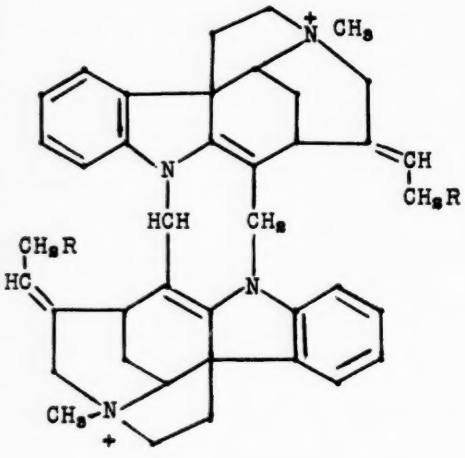
[2] K. Bernauer, F. Berlage, W. von Philipsborn, H. Schmid and P. Karrer, Helv. Chim. Acta 42, 201 (1959).

[3] F. Berlage, K. Bernauer, W. von Philipsborn, P. Waser, H. Schmid and P. Karrer, Helv. Chim. Acta 42, 394 (1959).

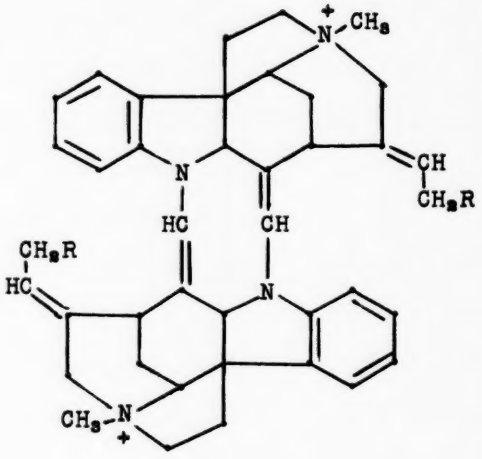
[4] A. R. Battersby and H. F. Hodson, Proc. Chem. Soc. (London) 287 (1958).

[5] A. R. Battersby and H. F. Hodson, J. Chem. Soc. 736 (1960).

[6] For recent summaries, see K. Bernauer, Fortschr. Chem. org. Naturstoffe 17, 184 (1959); and A. R. Battersby and H. F. Hodson, Quart. Rev. 14, 77 (1960).



I, R = -H
II, R = -OH



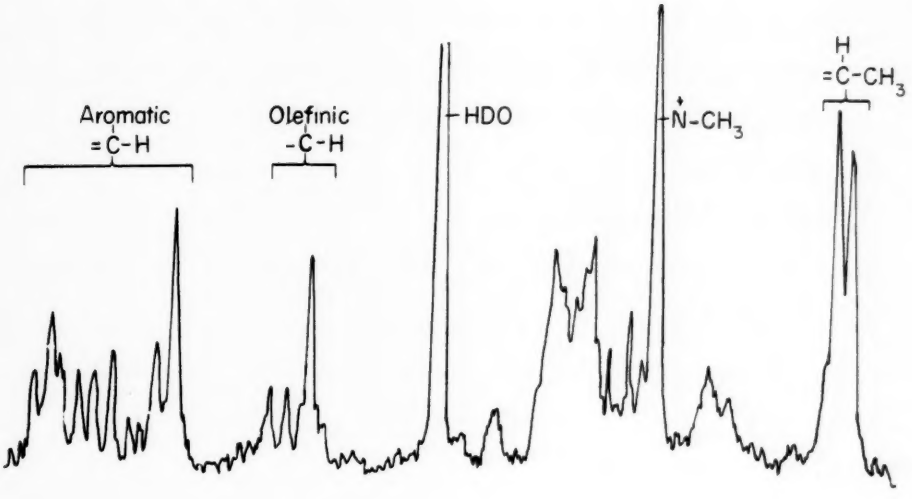
III, R = -H
IV, R = -OH

Because of the similarity of the ultraviolet absorption spectra of C-dihydrotoxiferine and C-toxiferine-I to that of known compounds containing the methyleneindoline chromophore, the Zurich and Bristol laboratories have favored structures I and II, respectively, for these alkaloids. However, since III and IV might be expected to exhibit rather similar absorption in the ultraviolet to I and II, this is not a satisfactory basis for deciding between these possibilities. Since nuclear magnetic resonance seemed particularly appropriate for deciding between I and III as possible structures for C-dihydrotoxiferine, we have synthesized a sample of this alkaloid and examined its nuclear magnetic resonance spectrum. Our preparation followed that reported by Schmid and Karrer and their collaborators and closely duplicated their results.[1,2] Also, the properties of

our material were in accord with those of a sample of dihydrotoxiferine isolated from calabash-curare of the Piaroa Indians.[7]

1960

Dihydrotoxiferine



N.M.R. Spectrum of C-Dihydrotoxiferine

For structure I, it would be expected that the signal in the olefinic region would be a quartet and correspond in area to one-fourth that of the aromatic protons; whereas, structure III

[7] A. Zurcher, O. Ceder and V. Boekelheide, J. Am. Chem. Soc. 80, 1500 (1958).

should show signals from two types of olefinic protons, one of which should be a quartet and the other a single sharp peak, with the total area of the olefinic protons being equal to one-half that of the signal for the aromatic protons. Examination of the NMR spectrum of C-dihydrotoxiferine chloride in the olefinic region shows an apparent quartet over which is superimposed a strong signal at -54 cps (relative to HDO). Furthermore, by electronic integration the area represented by the aromatic protons is twice that of the olefinic protons. Thus, the NMR spectrum of C-dihydrotoxiferine is in good accord with structure III but not for structure I.

Likewise, as we have suggested previously,[8] the NMR spectrum of C-toxiferine-I is in agreement with structure IV but not with structure II. Thus, the NMR spectrum of C-toxiferine chloride shows both a triplet and a singlet, each of equal area, in the olefinic region.

We are grateful to Professor David Wilson of the University of Rochester and Dr. L. F. Johnson of Varian Associates for the determination of spectra and for helpful discussions. The spectra were determined using deuterium oxide as solvent and a Varian V-4300C 60 Mc spectrometer. The details of these as well as other NMR studies of the calabash-curare alkaloids will be published shortly. We thank the National Institute of Neurological Diseases and Blindness of the National Institutes of Health (research grant B-671) and the Army Chemical Center for financial support.

---

[8] Lecture, University of Zurich, February, 1960.

Tetrahedron Letters No. 26, pp. 5-12, 1960. Pergamon Press Ltd. Printed in Great Britain

STRUCTURE OF VERBENALIN

G. Büchi and R. E. Manning

Department of Chemistry, Massachusetts Institute of Technology

Cambridge, Massachusetts, U. S. A.

(Received 17 November 1960)

VERBENALIN ($C_{17}H_{24}O_{10}$) m.p. 182-183° $[\alpha]_D^{25}$ -173° (H_2O), a glycoside isolated from Verbena officinalis has been the object of several chemical studies and all previous investigators agree that it is a β-D-glucoside. Although the presence of one keto group[1,2] and only one carbon-carbon double bond[1] seemed established, a structure containing a furan ring has been proposed.[3] There was further disagreement concerning the functionalities of the remaining oxygen atoms. One group[3] considered verbenalin to be a methyl ester while others[4,5] preferred a methoxylactone system which was incorporated into the most recent proposal (I)[5]. Catalytic reduction of verbenalin over platinized Raney-Nickel

---

1 J. Cheymol, Bull. Soc. Chim. 5, 633, 642 (1938).

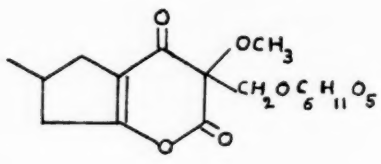
2 W. Hoffmann, Arch. Pharm. 281, 269 (1943).

3 J. Asano, Y. Ueno and Y. Tamaki, J. Pharm. Soc. Japan 62, 7 (1942).

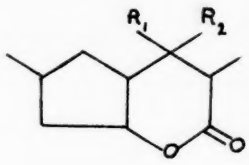
4 A. Chatterjee and L. M. Parks, J. Am. Chem. Soc. 71, 2249 (1949).

5 M. Cohn, E. Vis and P. Karrer, Helv. Chim. Acta 37, 790 (1954); P. Karrer and H. Salomon, Helv. Chim. Acta 29, 1544 (1946).

yields tetrahydroverbenalin m.p. 196-197° [Lit.[5] m.p. 195-196°] $\nu_{max.}^{KBr}$ 3300, 1713 cm^{-1} and desoxyverbanol ($C_{10}H_{16}O_3$) m.p. 139-140° [Lit.[5] m.p. 137-138°], $\nu_{max}^{CHCl_3}$ 3550, 1745 cm^{-1}, two C-Me groups (Kuhn-Roth). We have now oxidized desoxyverbanol with chromium trioxide in pyridine solution to desoxyverbanone m.p. 113-114°, $[\alpha]_D^{26}$ +57° ($CHCl_3$), $\nu_{max}^{CHCl_3}$ 1745 cm^{-1}, λ_{max}^{EtOH} 295 mμ ε 17. The negative ferric test and the infrared spectrum of this substance are inconsistent with III and consequently structures II and I proposed for desoxyverbanol and verbenalin, respectively require modification.



I



II R_1=OH; R_2=H

III R_1=R_2=O=

We assumed that verbenalin, the nepetalactones[6] and the iridomyrmecins[7] contain a common carbon skeleton and this was proved as follows. Desulfurization of desoxyverbanone-ethylene-thioketal m.p. 191-192°, $\nu_{max}^{CHCl_3}$ 1740 cm^{-1} with Raney-Nickel yielded

---

[6] R. B. Bates, E. J. Eisenbraun and S. M. McElvain, J. Am. Chem. Soc. 80, 3420 (1958) and earlier papers cited.

[7] G. W. K. Cavill and D. L. Ford, Austral. J. Chem. 13, 296 (1960) and references given there.

iridomyrmecin (IV) $[\alpha]_D^{26}$ +236° ($CHCl_3$) [Lit. [8,9] $[\alpha]_D^{20}$ +210° (CCl_4)] m.p. 60.5°-61.5° pure and mixed with an authentic specimen[10]. An infrared spectrum in nujol was identical with that of natural iridomyrmecin[9]. We have repeated the previously described hydrolysis of verbenalin with barium hydroxide and obtained verbenalinic acid now formulated as X m.p. 212-214° [Lit.[1] 210-212°] ν_{max}^{KBr} 1735, 1710, 1630 cm^{-1}; λ_{max}^{EtOH} 236 mμ (ε 6000) which however has the composition of $C_{16}H_{22}O_{10}$ rather than $C_{17}H_{26}O_{11}$[1]. In support of the formulation of verbenalin as a methyl ester esterification of X regenerated verbenalin (IX). Since the original glucoside contains one carboxyl function only the lactone grouping in desoxyverbanol (XII) originates from the carbomethoxy function in verbenalin which thus contains part structure V. Its ultraviolet spectrum, λ_{max}^{EtOH} 238 mμ (ε 9600) is similar to those of tetrahydro-desoxyplumieride (VII), λ_{max}^{EtOH} 236 mμ (ε 10000)[11] and bakankosin (VIII), λ_{max}^{EtOH} 236 mμ (ε 11600)[12] and if we accept this analogy an expanded formula (VI) results. Verbenalol (XIV)

---

8 R. Fusco, R. Trave and A. Vercellone, Chim e Industr. 37, 251 (1955).

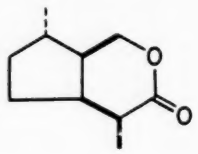
9 R. H. Jaeger and Sir Robert Robinson, Tetrahedron Letters 15, 14 (1959).

10 We are indebted to Dr. G. W. K. Cavill for this comparison.

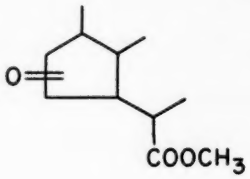
11 O. Halpern and H. Schmid, Helv. Chim. Acta 41, 1109 (1958).

12 G. Büchi, unpublished. K. Balenović, H. U. Däniker, R. Goutarel, M. M. Janot and V. Prelog, Helv. Chim. Acta 35, 2519 (1952).

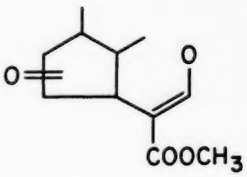
m.p. 125-128° (dec.) [Lit.[5] m.p. 124°], $\nu_{max}^{CHCl_3}$ 3550, 1750, 1710,



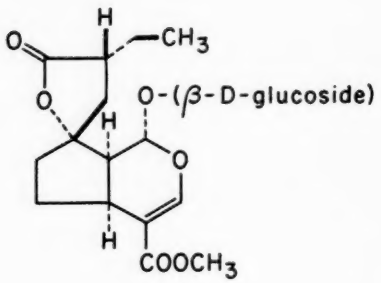
IV



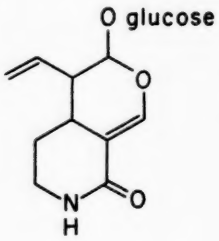
V



VI



VII



VIII

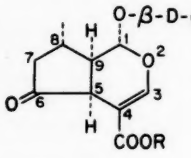
1640 cm^{-1}; λ_{max}^{EtOH} 240 mμ (ε 9050) available by emulsin catalyzed hydrolysis of the glucoside exhibits positive Fehling and Tollens tests. This behavior is explained by XIV and further evidence for the location of the hydroxyl group was provided by the ultraviolet spectrum which has λ_{max}^{EtOH} 271 mμ (ε 19000) in 0.01N sodium hydroxide solution. The bathochromic displacement observed (Δλ 31 mμ) is similar to that of ethyl acetoacetate (Δλ33 mμ)[13] and dihydrobakankogenin (Δλ 38 mμ)[12]. To complete the structure it

---

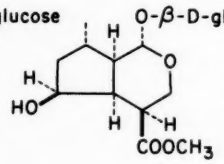
[13] P. Grossmann, Z. physik. Chem. 109, 305 (1924).

1960

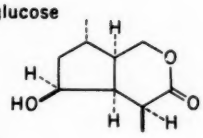
was necessary to place the ketone function which must be located on the cyclopentane ring. We have chosen C_6 for two reasons. (a) The formation of β-methylglutaric acid[5] on oxidation with three moles of ozone can only be rationalized with this alternative and (b) the high intensity n-π* transition in the ultraviolet spectrum of verbenalin, λ_{max}^{EtOH} 290 mμ (ε 105) is typical for



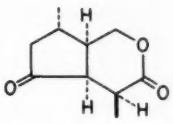
IX R = CH_3
X R = H



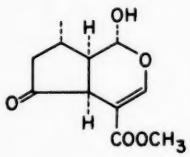
XI



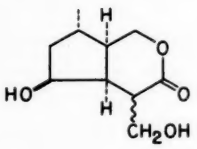
XII



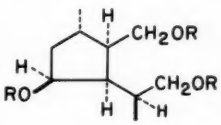
XIII



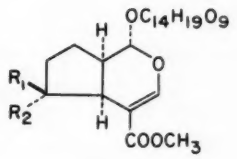
XIV



XV



XVI
R = NO_2
C_6H_4
CO



XVII
R_1 = OAc; R_2 = H

XVIII
R_1 = H; R_2 = OAc

non-planar β,γ-unsaturated ketones[14].

We shall now discuss the stereochemistry of verbenalin. The relative and absolute configuration of (+)-iridomyrmecin is known[7,9,15,16] and desoxyverbanone therefore has the configuration shown in XIII. Since reduction of desoxyverbanone (XIII) with sodium borohydride regenerates desoxyverbanol (XII) no isomerization had occurred during the reverse process and the configuration of XII is established. The previously described reconversion of verbenalinic acid (X) to verbenalin (IX) demonstrates that the natural product already contains a thermodynamically more stable cis-fused ring system. That the $\Delta^{5,6}$-enol was indeed formed during the saponification of IX to X was established in a separate experiment using deuterium oxide as a solvent. The verbenalin (IX) isolated after esterification with diazomethane and recrystallization from methanol contained 2.37 D atoms per molecule. It seems exceedingly unlikely that the configurations at both C_5 and C_9 were inverted in the course of catalytic reduction. The

---

[14] R. C. Cookson and N. S. Wariyar, J. Chem. Soc. 2302 (1956); H. Labhart and G. Wagniere, Helv. Chim. Acta 42, 2219 (1959); C. A. Grob and A. Weiss, Helv. Chim. Acta 43, 1390 (1960); G. Büchi and E. M. Burgess, J. Am. Chem. Soc. 82, 4333 (1960).

[15] L. Dolejš, A. Mironov and F. Šorm, Tetrahedron Letters 11, 18 (1960). E. J. Eisenbraun, T. George, B. Riniker and C. Djerassi, J. Am. Chem. Soc. 82, 3648 (1960).

[16] G. W. K. Cavill, personal communication.

1960

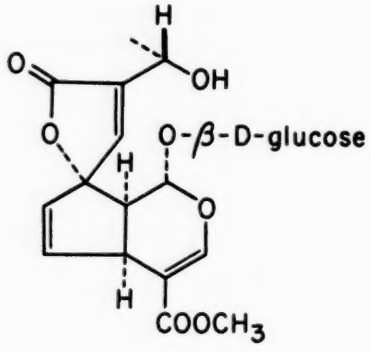
molecular rotation difference $[M]_D$ tetrahydroverbenalin-$[M]_D$ tetrahydroverbenalol is -448° (in water) and that for $[M]_D$ hexahydrodesoxyplumieride - $[M]_D$ of the corresponding aglucone is -325° (in methanol[11]). This tentatively suggests α-configuration for the glucose at C_1.

Catalytic reduction of verbenalol (XIV) takes a different course and yields norverbanol ($C_{10}H_{16}O_4$) (XV) m.p. 97-98.5° [Lit.[5] 95-96°], $\nu_{max}^{CHCl_3}$ 3500, 1750 cm^{-1} containing one C-Me group (Kuhn-Roth). Its monotosylate m.p. 127.5-128° on reduction with lithium aluminum hydride followed by reaction with p-nitrobenzoyl chloride gave the triester XVI m.p. 174-176° which could also be prepared by hydride reduction and esterification of desoxyverbanol (XII).

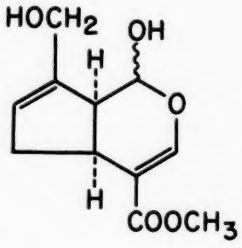
We have also synthesized the two epimeric pentaacetates XVII and XVIII. Treatment of verbenalin with sodium borohydride in absolute methanol produced a crude pentol which was transformed further to XVII m.p. 172-174°, ν_{max}^{KBr} 1735, 1700, 1645 cm^{-1}, λ_{max}^{EtOH} 232 mμ (ε 11200) by acetylation. Tetraacetylverbenalin m.p. 133-134° [Lit.[5] 133°], $\nu_{max}^{CHCl_3}$ 1750, 1710, 1640 cm^{-1}, λ_{max}^{EtOH} 235 mμ (ε 9370) was reduced with sodium borohydride and the resulting pentoltetraacetate transformed to the tetraacetyl monotosylate m.p. 157-158°. Conversion to XVIII m.p. 134-138°, ν_{max}^{KBr} 1750, 1705, 1635 cm^{-1}, λ_{max}^{EtOH} 234 mμ (ε 11500) was achieved by warming the tosylate with tetraethylammonium acetate in acetone solution. Both XVII and XVIII were different from loganinpenta-

acetate[17] m.p. 137-138° (mixed melting points and infrared spectra)[18].

Verbenalin is biogenetically related to (-)-plumieride[11] (XIX) and genipin[19] (XX).



XIX



XX

We are indebted to the National Science Foundation (Research Grant G 7424) for financial support, to Dr. T. Carney of Eli Lilly and Company for the extraction of verbenalin and to Dr. J. K. Sutherland and Prof. R. B. Woodward for a stimulating discussion.

---

17 A. J. Birch and E. Smith, Austral. J. Chem. 9, 234 (1956). K. W. Merz and H. Lehmann, Arch. Pharmaz. 290, 543 (1957).

18 We wish to thank Dr. J. Grimshaw, Manchester, for samples of loganin from Strychnos lucida and its pentaacetate.

19 C. Djerassi, T. Nakano, A. N. James, L. H. Zalkow, E. J. Eisenbraun and J. N. Shoolery, J. Org. Chem. in press.

Tetrahedron Letters No. 26, pp. 13-17, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

THE STRUCTURE OF SKATOLE DIMER. NEW REACTIONS OF INDOLINE DERIVATIVES

Giancarlo Berti, Antonio Da Settimo and Domenico Segnini
Institute of Pharmaceutical Chemistry, University of Pisa
Pisa, Italy

(Received 31 October 1960)

IN connection with our work on the determination of the base strengths of indole derivatives,[1] it became of importance to study the dimers which some of these compounds form in acidic solutions. While structure I was definitely proved for indole dimer,[2] no recent data were available on skatole dimer, although its structure had been a matter of dispute between Oddo,[3] who proposed a pentacyclic formula, and Schmitz-Dumont,[4] who favoured instead the more likely formulation II, but did not give a real proof for it. A structure similar to that of diindole (I) was evidently impossible for diskatole, but III seemed to be a possible alternative for II, on the basis of our results on the comparative basicities of indole and its methyl derivatives.[1] We have now succeeded in proving that III is the structure of diskatole. In a recent paper No-

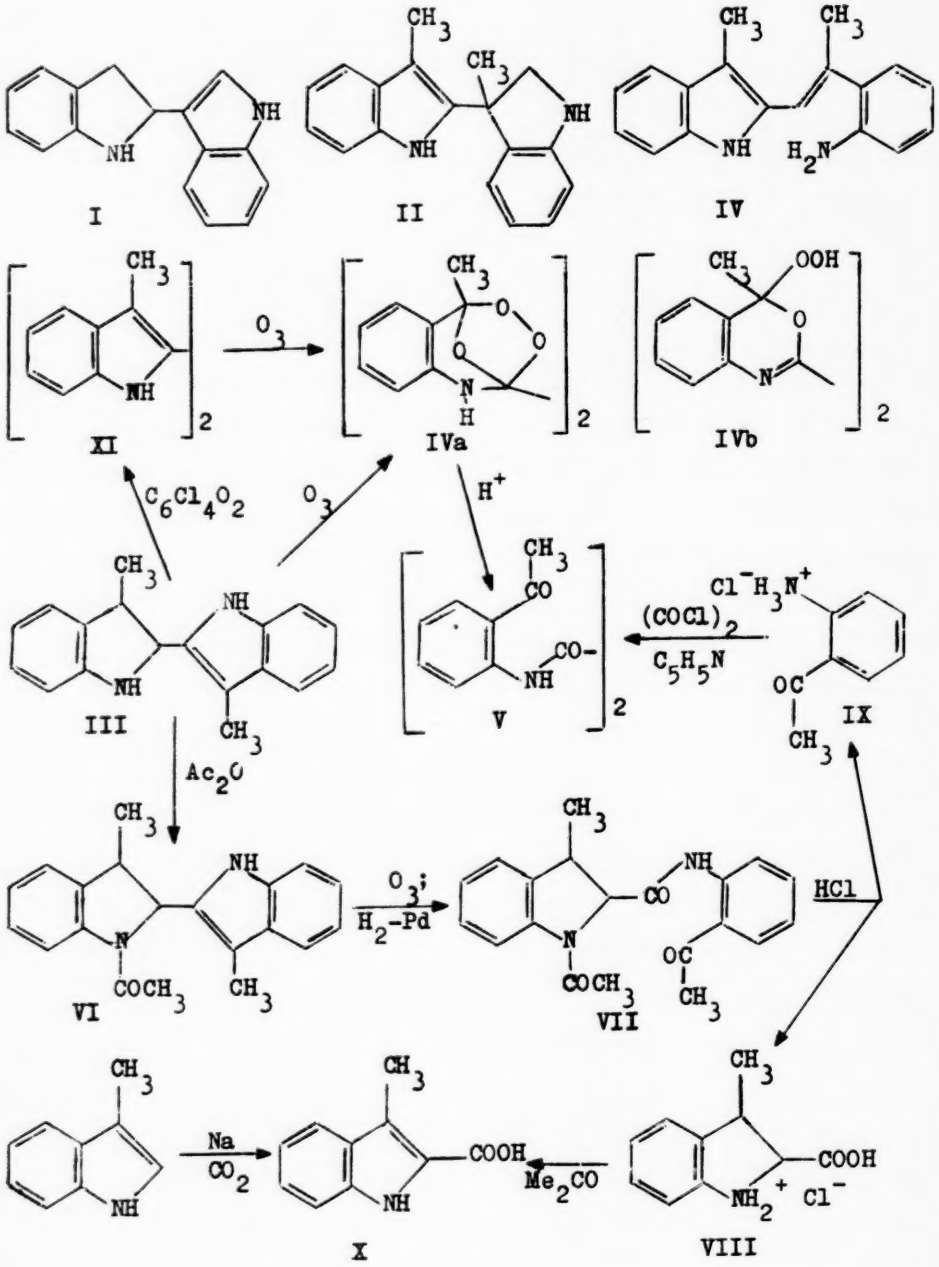
---

[1] G. Berti, A. Da Settimo and D. Segnini, Ricerca Sci. 30, 1057 (1960).

[2] H.F.Hodson and G.F.Smith, J. Chem. Soc. 3544 (1957).

[3] B. Oddo, Gazz. Chim. Ital. 43, 898 (1933).

[4] O. Schmitz-Dumont, Liebigs Ann. 514, 267 (1934).


I
II
IV
XI
IVa
IVb
$C_6Cl_4O_2$
O_3
H^+
III
V
$(COCl)_2$
C_5H_5N
IX
Ac_2O
VI
O_3; H_2-Pd
VII
HCl
Na
CO_2
X
Me_2CO
VIII

land and Hammer [5] mentioned that they had been privately informed by G.F. Smith and A.E. Walters, that diskatole has structure III, but did not give any detail on how this was demonstrated. As some unusual reactions were encountered during our work, we are reporting briefly on our proofs of structure.

1960

When a stream of ozonised oxygen was passed through a solution of diskatole in ethyl acetate, a stable ozonide (m. p. 160°) precipitated in 22% yield. Several cases of stable ozonides, derived from 2:3-disubstituted indoles, are known.[6-10] The analysis of our compound, however, showed that it was a diozonide, instead of the expected simple ozoride (found: C, 60.78; H, 4.89; N, 7.41. $C_{18}H_{16}O_6N_2$ requires:C, 60.67; H, 4.53; N, 7.86%). This result could have been explained by a structure of diskatole with two reactive double bonds, such as IV, a not completely unlikely hypothesis if one considers the structure of triindole.[11] However, it is known that diskatole

---

[5] W.E. Noland and C.F. Hammer, J. Org. Chem. 25, 1525 (1960).

[6] P. Karrer and P. Enslin, Helv. Chim. Acta 32, 1390 (1949).

[7] C. Mentzer, D. Molho and Y. Berguer, Bull. Soc. Chim. Fr. 555 (1950).

[8] B. Witkop and J.B. Patrick, J. Amer. Chem. Soc. 74, 3855 (1952).

[9] B. Witkop, J.B. Patrick and H.M. Kissman, Ber. Dtsch. Chem. Ges. 85, 949 (1952).

[10] D.W.Ockenden and K. Schofield, J.Chem.Soc. 612 (1953).

[11] G.F. Smith, Chem. and Ind. 1451 (1954); W.E. Noland and W.C. Kuryla, J. Org. Chem. 25, 486 (1960).

forms a dinitroso derivative;[12] now we have found that it gives an alkali insoluble toluenesulphonamide, m.p. 193°, and, with an excess of methyl iodide, a quaternary iodide, with two methyl groups more than the starting compound (m.p. 204-206°; found: C, 57.29; H, 5.44. $C_{20}H_{23}N_2I$ requires: C, 57.42; H, 5.54%); all this proves the absence of a primary amino group and rules out structure IV.

When the ozonide was treated with acetic acid, or with sulphuric acid in tetrahydrofuran, it was transformed into compound V (m.p. 267-270°; found: C, 66.54; H, 4.97; N, 8.36. $C_{18}H_{16}O_4N_2$ requires: C, 66.66; H, 4.97; N, 8.64%), which was also prepared from o-aminoacetophenone and oxalyl chloride. The formation of V proved the structure IVa (or IVb [9]) for the ozonide and showed that the ozonisation of diskatole follows, at least in part, an unusual course, involving a dehydrogenation of the indoline ring by the ozone, 2:2'-diskatyl being a possible intermediate. The dehydrogenation is not caused by the oxygen mixed with the ozone, as diskatole was recovered unchanged after a two-hour treatment with oxygen; peroxides were not formed, in contrast with the behaviour of 2-phenylskatole.[8] The unknown 2:2'-diskatyl (XI) was easily prepared from diskatole with chloranil in benzene (m.p. 162-163°; found: C, 83.35; H, 6.26. $C_{18}H_{16}N_2$ requires: C, 83.04; H, 6.20%); it gave the same ozonide as diskatole, in 45% yield. Although the results described above pointed strongly to structure III for skatole dimer, we did not think it safe to base our proof only on

---

[12] O. Schmitz-Dumont, K. Hamann and K.H. Geller, Liebigs Ann. 504, 1 (1933).

a new reaction of low yield and unknown mechanism, which could even involve some rearrangement.

When the monoacetyl derivative of diskatole (VI) was ozonised, no stable ozonide was isolated (apparently, the abnormal reaction requires a free imino group in the indoline moiety); the ozonised solution was hydrogenated over palladium and compound VII was obtained in 70% yield (m.p. 126-127°; found: C, 71.39; H, 5.87. $C_{20}H_{20}O_3N_2$ requires: C, 71.41; H, 5.99%). It was hydrolysed by hydrochloric acid to a mixture of o-aminoacetophenone hydrochloride (IX) and of the hydrochloride VIII (m.p. 122°, sint. at 98°; found: C, 51.56; H, 6.38; N, 6.24. $C_{10}H_{11}O_2N.HCl.H_2O$ requires: C, 51.84; H, 6.09; N, 6.05%); the latter compound, when heated <u>in vacuo</u> at 80°, gave the free acid (m.p. 154-156°; found: C, 67.63; H, 6.40. $C_{10}H_{11}O_2N$ requires: C, 67.78; H, 6.26%), whose structure was proved through another unusual dehydrogenation reaction: the acid or its hydrochloride, dissolved in acetone, were transformed, after a few hours at room temperature, into another acid, m.p. 163-165°, which was shown to be skatole-2-carboxylic acid (X) by comparison of its infra-red spectrum with that of a sample prepared from skatole with sodium and carbon dioxide.[13] Structure III was thus definitely proved for the dimer of skatole. The facile dehydrogenations of indoline derivatives shown by reactions III → IVa (or IVb), III → XI and VIII → X, which should be due to a considerable gain in resonance stabilisation, caused by the formation of a new double bond, linking two unsaturated systems, deserve further study; work along these lines is in progress at present.

---

[13] G. Ciamician and G. Magnanini, <u>Ber. Dtsch. Chem. Ges.</u> <u>21</u>, 1925 (1888).

THE MOLECULAR STRUCTURE AND ABSOLUTE CONFIGURATION OF THELEPOGINE METHIODIDE

J. Fridrichsons and A. McL. Mathieson

Division of Chemical Physics, C.S.I.R.O. Chemical Research Laboratories, Melbourne, Australia.

(Received 14 November 1960)

An alkaloid has been isolated from the grass, Thelepogon elegans, by Dr. W. D. Crow* of the Organic Chemistry Section of the Chemical Research Laboratories, C.S.I.R.O. and named thelepogine[1]. Since only a small amount of the alkaloid was available and this X-ray analysis was proposed, no investigation of the structure by chemical or other physico-chemical techniques was initiated apart from elemental analysis of the base and its methiodide. Excellent crystals of the methiodide were provided by Dr. Crow, the microanalytical data being in closest accord with $C_{20}H_{33}ON.CH_3I$.

The crystals are monoclinic with a = 7.462, b = 13.044, c = 11.117Å, β = 109.05° at -150°C, the space group being $P2_1$ with two molecules in the unit cell. X-ray analysis (CuK_α radiation) was based on only the $h0l$, $0kl$ and $1kl$ data (704 reflections of 764 theoretically possible). The molecular skeleton i.e. atoms other than hydrogen, was first located three-dimensionally and then the nitrogen and oxygen atoms differentiated. From the bond lengths and stereochemical disposition within the skeleton, hydrogen atom sites

---

*Present address: Chemistry Department, Australian National Univ. Canberra, Australian Capital Territory, Australia.

[1] W. D. Crow — to be published.

can be allocated, the molecular formula on this basis being $C_{20}H_{31}ON.CH_3I$. With the molecular structure defined, the absolute configuration of the molecule was fixed by application of Bijvoet's[2] technique using the anomalous dispersion of the iodine atoms.

The atomic distribution of the molecular skeleton as viewed down the b axis is given in the correct absolute orientation in Fig. 1a while a more conventional chemical formulation is presented in Fig. 1b.

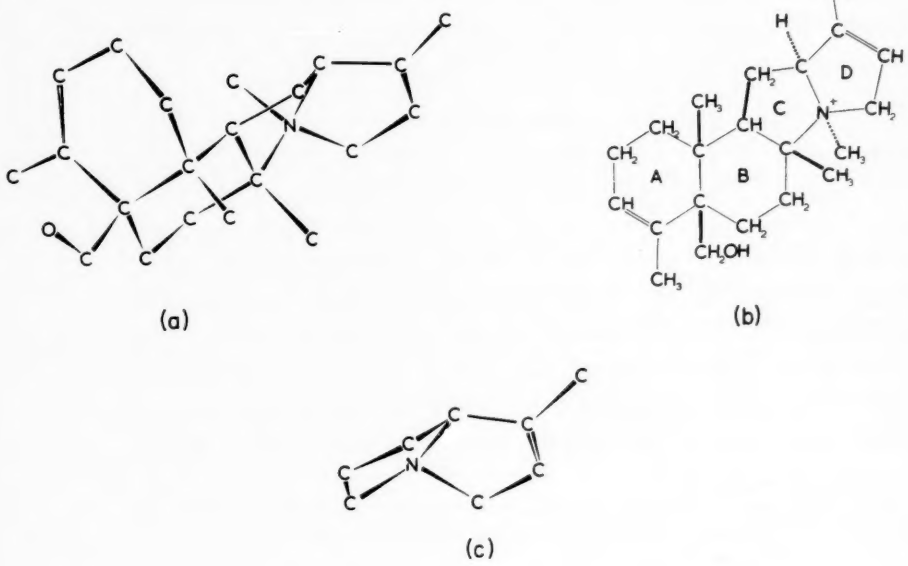


FIG. 1.

[2] J. M. Bijvoet, A. F. Peerdeman and A. J. van Bommel, Nature 168, 271 (1951).

As an example of structure-determination by the X-ray technique based only on knowledge of the empirical formula[3], a more complete discussion of the analysis of this grass alkaloid will be presented later but certain observations on the structure may be of more immediate chemical interest.

a) The molecule of thelepogine contains within its atomic array the skeleton of the pyrrolizidine ring systems, CD in Fig. 1b. Comparison of the three-dimensional ball model of the thelepogine methiodide structure with that for jacobine bromhydrin[4] reveals that the pyrrolizidine ring systems exhibit unexpected coincidence of structural detail e.g. location of the double bond, substitution in the 1-position (pyrrolizidine convention) and, in particular, their absolute configuration. Fig. 1c presents the retronecine component of the jacobine bromhydrin structure[4] for comparison.

b) That the molecular formula of the alkaloid involves a C_{20} component suggested the probability of a diterpenoid origin for thelepogine. Thus the carbon skeleton of thelepogine may be derived from a hypothetical precursor of the manno81[5] type, Fig. 2a, by a 1,2 shift of the β-methyl group from the 4-position to the 5β-position resulting in the formation of the 3,4 double bond, Fig. 2b. Ring closure of the side chain could be affected by the introduction of nitrogen in a manner analogous to that in Adams and Leonard's[6] synthesis of (-)-retronecanone. Subsequent elimination of the hydroxyl group from C_{13} could give rise to the 13,14 double bond.

---

[3] A. McL. Mathieson, I.U.P.A.C. Symposium on the Chemistry of Natural Products, Australia (1960) (to be published by Butterworths Scientific Publications, London).

[4] J. Fridrichsons, A. McL. Mathieson and D. J. Sutor, Tetrahedron Letters No. 23, 35 (1960).

[5] Ann. Reports Chemical Society 60, 243 (1958).

[6] R. Adams and N. J. Leonard, J. Amer. Chem. Soc. 66, 257 (1944).

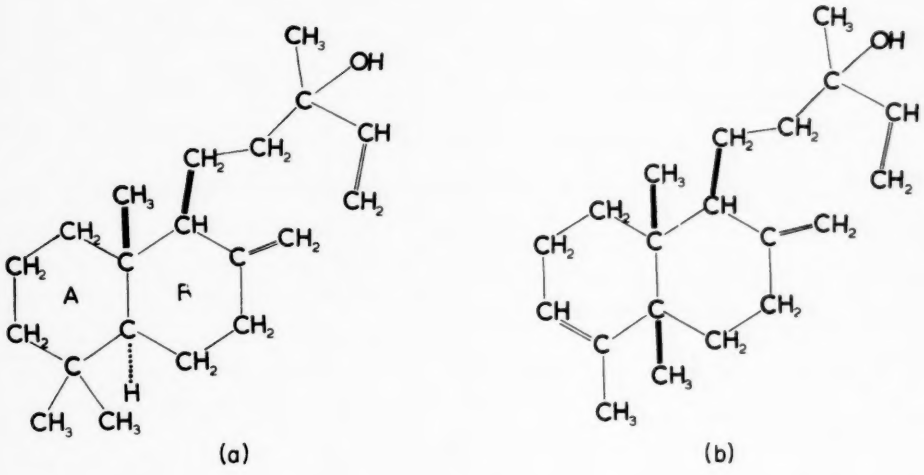


FIG. 2.

Such a scheme would account for the identity of the asymmetric centres common to thelepogine and the mannoöl derivative cf. Figs. 1b and 2b. These structural relations with diterpenes have been discussed with Dr. C. S. Barnes of the Organic Chemistry Section for whose assistance we are grateful.

Tetrahedron Letters No. 26, pp. 22-24, 1960. Pergamon Press Ltd. Printed in Great Britain

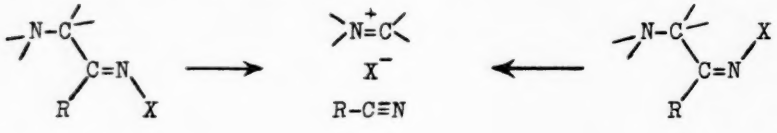
SYNCHRONE CIS-ELIMINIERUNG BEI DER FRAGMENTIERUNG VON SYN α-AMINO-ACETOPHENON-OXIMEN

Hp. Fischer und C.A. Grob

Organisch-chemisches Institut der Universität Basel

(Received 3 November 1960)

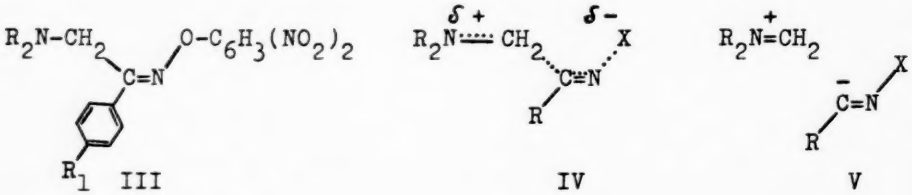
Die anti und syn Formen der Ester und Aether von α-Aminoketoximen I bzw. II stellen fragmentierbare Systeme dar,[1] welche besonders in polaren Lösungsmitteln vollständig in Nitrile und Carbimoniumsalze zerfallen.



I II

X = $-OSO_2C_6H_4CH_3$; $-OC_6H_3(NO_2)_2$; $-OCOC_6H_5$

Bei anti Oximen I, welche eine anti-parallele Anordnung der beteiligten Elektronenpaare aufweisen, wurde ein synchroner Mechanismus der Fragmentierung angenommen, weil die Reaktionsgeschwindigkeit (RG) vom elektromeren Effekt der α-Aminogruppe abhing.[2,3]



III IV V

---

[1] C.A. Grob, Theoretical Organic Chemistry, Proceedings of the Kekule Symposium, London 1958, Seite 114.

[2] Hp. Fischer, C.A. Grob & E. Renk, Helv.Chim.Acta 42, 872 (1959).

[3] C.A. Grob, Bull.Soc.chim.France 1360 (1960).

RG-Konstanten[a] der Solvolyse von syn α-Aminoacetophenon-oxim-2,4-dinitrophenyl-äther (III) in 80-Vol.-proz. Aethanol bei 70°.

NR_2	R	k (sec^{-1})	k_{rel}
	H	$1{,}56\ 10^{-3}$	1
$-N(CH_3)CH_2C_6H_5$	H	$1{,}26\ 10^{-3}$	0,81
	H	$1{,}04\ 10^{-4}$	0,067
$-NH_2$	H	$1{,}08\ 10^{-5}$	0,0069
-H	H	ca.$1\ 10^{-8}$	ca. $10^{-5,2}$
	NO_2	$1{,}73\ 10^{-4}$	0,11

[a] konduktometrisch gemessen.

In den entsprechenden syn Oximderivaten II sind die beteiligten Bindungen nicht mehr anti-parallel. Trotzdem sind, wie die Tabelle zeigt, die RG-Konstanten der 2,4-Dinitrophenyläther von syn α-Aminoacetophenonoxim-derivaten III in 80-proz. Aethanol im Vergleich zu entsprechenden Acetophenonoxim-derivaten III (H statt NR_2) enorm beschleunigt und wiederum deutlich vom elektromeren Effekt der Aminogruppe abhängig. Doch reagieren die syn Formen bei 70° ca. 1800 mal langsamer als die entsprechenden anti Formen, wie ein Vergleich der RG-Konstanten der syn und anti Formen des Piperidino-acetophenon-oxim-benzoates (k_{syn} $7{,}37\ 10^{-5}$; k^{b}_{anti} $1{,}3\ 10^{-1}$) bei 70° zeigt.

Diese Befunde sprechen dafür, dass auch die syn α-Aminoketoxim-derivate nach einem synchronen Mechanismus reagieren. Während aber die Fragmentierung von anti Oximen I einer norma-

[b] extrapoliert

len trans Eliminierung entspricht, stellt sie im Falle der syn Oxim-derivate II bzw. III den ungewöhnlichen Fall einer synchronen cis-Eliminierung dar. Der im Vergleich zur entsprechenden anti Form stereoelektronisch ungünstigere Uebergangszustand IV bedingt eine um ca. 5 Kcal/Mol höhere freie Aktivierungsenergie. Bei syn Acetophenonoxim-derivaten III (H statt R_2N) tritt statt der Fragmentierung Verbrückung und Wanderung des trans-ständigen Phenylrestes unter Bildung von Amiden ein.[4]

Da die relative RG in der syn-Reihe III von der Natur der Aminogruppe und der Abgangsgruppe abhängt und nur wenig von einer p-Nitrogruppe im Phenylrest (III, $R_1 = NO_2$) beeinflusst wird, kann die früher vermutete RG-bestimmende Isomerisierung[2] zur entsprechenden anti Form ausgeschlossen werden. Ferner ist ein langsamer Zerfall in ein Carbimonium-ion und ein Carbanion V,[5] welches anschliessend die Abganggruppe X eliminiert, unwahrscheinlich. In diesem Fall müsste eine starke Beschleunigung der Reaktion durch eine p-Nitrogruppe (III, $R_1 = NO_2$) eintreten, während tatsächlich eine Verlangsamung beobachtet wird (vergl. Tabelle).

---

[4] R. Huisgen et al., Liebigs Ann. Chem. 604, 191 (1957).

[5] vergl. S.J. Cristol & W.P. Norris, J.Amer.chem.Soc. 76, 3005 (1954).

Tetrahedron Letters No. 26, pp. 25-29, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

ACETYLENIC OXYGEN HETEROCYCLES[1]

Franz Sondheimer, Yehiel Gaoni and
Judith Bregman
Daniel Sieff Research Institute, Weizmann
Institute of Science, Rehovoth, Israel

(Received 8 November 1960)

IN 1929 Lespieau[2] reported that dichlorodimethyl ether (I) on reaction with acetylenedimagnesium bromide yielded ca. 2% of 1,6-dioxa-3,8-cyclodecadiyne (II), a ten-membered heterocyclic diacetylene. Since no structure proof was given, this work has subsequently either been discounted[3] or else disregarded [e.g. by Treibs and Pester[4] who very recently described a synthesis of the related heterocycle (III, n = 6) by a method which could not be adapted to the preparation of (III, n = 4), a tetrahydro-derivative of (II)]. Some time ago we re-

---

[1] This is Part XVI in the Series "Unsaturated Macrocyclic Compounds". For Part XV, see F. Sondheimer and Y. Gaoni, J. Amer. Chem. Soc. in press.

[2] R. Lespieau, Compt. rend. 188, 502 (1929).

[3] See D.J. Cram and N.L. Allinger, J. Amer. Chem. Soc. 78, 2518 (1956).

[4] W. Treibs and R. Pester, Tetrahedron Letters No. 17, 5 (1960).

investigated the reaction of Lespieau[2] and carried out a number of new reactions with the product corresponding in properties to those reported for (II). Our work conclusively shows the structural assignment of Lespieau to be correct and the credit for preparing the first cyclic acetylene must therefore be given to this investigator.

The reaction of (I) with an equimolecular amount of acetylenedimagnesium bromide in benzene afforded a product which on direct crystallization and chromatography of the mother liquors on alumina yielded a total of ca. 2% of (II) as colorless prisms (Anal. Calcd. for $C_8H_8O_2$: C, 70.57; H, 5.92; mol. wt., 136. Found : C, 70.55; H, 5.76; mol. wt., 136[5]). This substance showed m.p. 170-172° dec. when placed between two cover slides on a rapidly heated Fisher-Johns block at ca. 165° (decomposition without melting occurred if put on block before). A sample sublimed without melting when placed on an open cover slide in the range 100-180°, but from ca. 180° melting occurred; this corresponds to the observation of Lespieau[2] that (II) melted on the "bloc Maquenne" at about 180°. The infrared spectrum (in KBr) was compatible with structure (II) [strong bands at 9.03 and 9.37 μ (C-O vibration);

---

[5] Determined by the thermistor-drop technique, in methylene chloride (see B.R.Y. Iyengar, Rec. Trav. Chim. 73, 789 (1954).

1960

CH2Cl
CH2Cl
I
CH2-C≡C-CH2
CH2-C≡C-CH2
II
CH2-C≡C-CH2
(CH2)n
III
CH2COOH
CH2COOH
VI
(CH2)4
(CH2)4
V
CH=CH
CH=CH
IV
CH2-O-CH2-C≡C-CH2
CH2-C≡C-CH2
VII
CH2-C≡C-CH2
CH2-C≡C-CH2
II b
CH2-C≡C-CH2
CH2-C≡C-CH2
II a

weak band at 4.75 μ (disubstituted acetylene or overtone of the 9.37 μ band)] and showed the absence of allene or terminal acetylene groupings. There was only end-absorption in the ultraviolet.

Partial hydrogenation of (II) in benzene over a Lindlar palladium catalyst[6] led to cis-cis-1,6-dioxa-3,8-cyclodecadiene (IV) as prisms, m.p. 117-118° (between two cover slides; sublimes without melting at 70-80° on an open cover slide), showing a strong cis-ethylene band at 13.40 μ in the infrared (Anal. Calcd. for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found : C, 68.53; H, 8.74). Full hydrogenation of (II) in ethyl acetate over platinum resulted in the uptake of exactly 4 molar equivalents of hydrogen and yielded 1,6-dioxacyclodecane (V), b.p. 90-100° (bath temp.) (25 mm.), n_D^{28} 1.4542 (Anal. Calcd. for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found : C, 66.48; H, 10.93).

Oxidation of (II) in acetone with aqueous potassium permanganate at 3° produced diglycolic acid (VI), m.p. 145-146°, identified with an authentic sample (m.p. 146-147°).

The two conformations (IIa) and (IIb) are possible for (II). The X-ray diffraction data (space group $P2_1/c$; a = 6.82 Å, b = 7.72 Å, c = 6.98 Å, β = 113.8°) and measured density of 1.33 identify the asymmetric unit in the unit cell as C_4H_4O. Symmetry requirements of the space group eliminate any multiple (n) of this unit higher than n = 2. Since n = 1

---

[6] H. Lindlar, Helv. Chim. Acta 35, 446 (1952).

is ruled out by the molecular weight determination, the molecule is identified as $C_8H_8O_2$ having a molecular center of symmetry. Hence, in this particular crystal structure at least, the molecules are present in the chair conformation (IIa) and not in the boat (IIb).

1960

The reaction of (I) with acetylenedimagnesium bromide in addition to (II) produced another substance in ca. 0.5% yield (eluted from the chromatogram directly after (II)), which crystallized as long colorless laths, m.p. 68-69°. This second product must be the fifteen-membered acetylenic heterocycle 1,6,11-trioxa-3,8,13-cyclopentadecatriyne (VII) in view of the elemental analysis and molecular weight determination (Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92; mol. wt., 204. Found : C, 70.68; H, 6.00; mol. wt., 192, 194[5]) as well as the similarity of the infrared spectrum to that of (II).

We are investigating at present the application of the Lespieau type of reaction for the synthesis of other heterocyclic and carbocyclic acetylenes.

Acknowledgments. We are indebted to Dr. V.M. Clark and Mr. G. Purdy of Cambridge University for the molecular weight determinations.

Tetrahedron Letters No. 26, pp. 30-34, 1960. Pergamon Press Ltd. Printed in Great Britain

SOLVOLYSIS OF OZONIDES

Erling Bernatek and Tore Ledaal

Universitetets Kjemiske Institutt

Blindern-Oslo Norway

(Received 8 November 1960)

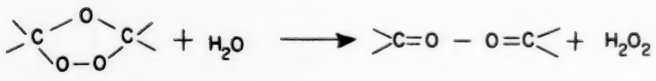
Decomposition of ozonides or ozonisation mixtures has been attained with a great variety of reagents and over a wide range of reaction conditions. The methods can be divided into three main categories; viz. oxidative, reductive and solvolytic decompositions.

While the oxidative methods have been investigated and used to a fair degree, a special importance is attached to the reductive methods, since the desired products from ozonolyses are often sensitive aldehydes. Experimental details have been reviewed by Long[1] and Bailey[2]. Solvolytic decompositions, on the other hand, do not seem to have been subjected to systematic investigations, the only example known so far being hydrolysis.

Solvolysis of an ozonide can be defined as a reaction where the active oxygen of the ozonide is transferred to the solvent and retained by it as such. In the case of hydrolysis the overall reaction may be represented as follows:

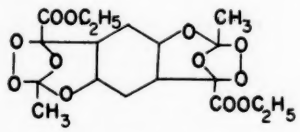
---

[1] Long, L. Jr. Chem.Revs. 27 (1940) 437.
[2] Bailey, P.S. Chem.Revs. 58 (1958) 925.

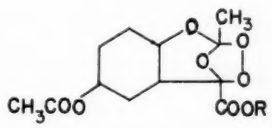


The active oxygen is transferred to water and retained in its active state in hydrogen peroxide.

In principle there is no reason why this type of reaction should not be extended to other solvents capable of incorporating active oxygen. It is a commonplace that a number of organic acids can take up an additional oxygen atom in the carboxyl group, thereby forming peracids. We considered it possible that carboxylic acids could also acquire an active oxygen from ozonides under suitable circumstances. Experiments were therefore carried out on the acidolysis of the stable ozonides I - IV.[3-5]



I

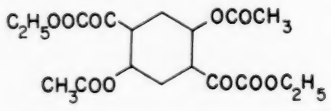


II: R = CH_3; III: R = C_2H_5; IV: R = C_3H_7

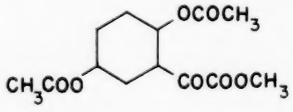
When dissolved in formic acid (98-100%) at room temperature, I and II smoothly formed performic acid which could be distilled

[3] Bernatek, E. and Thoresen, F. Acta Chem. Scand. 9 (1955) 743.
[4] Bernatek, E. and Bø, I. . Acta Chem. Scand. 13 (1959) 337.
[5] Bernatek, E. and Hvatum, M. Acta Chem. Scand. 14 (1960) 836.

off in vacuo and amounted to 62 and 45% of theoretical respectively. The somewhat low yield is partly attributed to decomposition of peracid in the vapour phase. The distillation residues contained no active oxygen and from I the expected reduction product V was isolated in good yield.



V



VI

In glacial acetic acid the solvolysis proceeded tardily at room temperature, but the addition of catalytic amounts of perchloric acid accelerated the reaction. Distillation in vacuo afforded peracetic acid in 78, 60 and 60 % yield from the ozonides I, II and IV respectively. Again the content of active oxygen in the residues was nil and from I and II the reduction products V and VI were isolated in good yield.

Peracids could also be determined directly in the reaction mixture by diluting aliquots with large volumes of ice-water, adding potassium iodide and titrate rapidly with sodium thiosulphate[6]. It was found in this way that ozonides II and

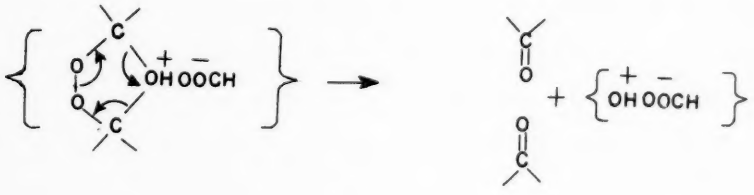
[6] Hatcher, W.H. and Holden, G.W. Trans.Roy.Soc. Canada 21 (1928) 238.

1960

III in formic acid gave 87 and 93 % of performic acid. In acetic acid containing perchloric acid the ozonides I and III gave 86 and 97 % of peracetic acid.

Qualitative experiments were performed with propionic and dichloroacetic acids. Propionic acid needed perchloric acid as a catalyst and gave then with I and II ample amounts of perpropionic acid. Dichloroacetic acid, on the other hand, reacted smoothly without a catalyst forming peracid. Some side-reaction also occurred in this case imparting a dark colour to the reaction mixture.

The acidolysis of ozonides is probably a specific proton-catalysed reaction. From considerations of the basicity of the atoms in the ozonide ring the proton attack is most likely to take place at the ether oxygen. The protonated ozonide and e.g. a formate ion can form an ion-pair VII which by a concerted



VII VIII

collapse as indicated by the arrows forms two carbonyl groups and a new ion-pair VIII. The latter will of course immediately combine to performic acid.

Acidolysis, especially formolysis, may turn out to be a valuable method in decomposing ozonides which are only slowly attacked by water or are slightly soluble in aqueous solutions. Preliminary experiments indicate that no other organic peroxy compounds undergo the acidolysis reaction with the formation of peracids and work is in progress concerning the exploitation of the reaction as a diagnostic test for ozonides.

Tetrahedron Letters No. 26, pp. 35-41, 1960. Pergamon Press Ltd. Printed in Great Britain

THE INFRA-RED SPECTRUM OF $\left[C_4H_4.Ag\right] NO_3$

H.P. Fritz, J.F.W. McOmie and N. Sheppard

Institut für Anorganische Chemie, Universitat München, W. Germany (H.P.F.)

Department of Organic Chemistry, The University, Bristol, England, (J.F.W.M.)

University Chemical Laboratory, Cambridge, England, (N.S.)

(Received 8 November 1960)

IN this note we wish to report preliminary results from the analysis of the infra-red spectrum of cyclobutadiene silver nitrate $\left[C_4H_4Ag\right] NO_3$[1] in relation to possible structures for the complex cation.

Table 1 shows the spectrum obtained with Unicam SP100 and Perkin-Elmer Model 21 spectrophotometers using LiF. NaCl and Cs Br optics and polycrystalline samples mulled in nujol, hexachlorobutadiene and fluorolube. Another spectrum obtained in a KBr disc showed evidence of decomposition of the complex.

---

[1] M. Avram, E. Marica and C.D. Nenitzescu, Chem.Ber. 92, 1088 (1959).

The primary purpose of the investigation was to define the nature of the hydrocarbon ligand, and the first consideration is whether this has the formula C_4H_4 or C_8H_8. Dimeric structures have to be considered because a hydrocarbon of this formula is evolved on treatment of the complex with sodium chloride[2] and also because the overall spectrum is of some complexity. However whereas the silver nitrate complex shows only two bands in the ethylenic CH region, the evolved hydrocarbon shows a prominent third band in the saturated CH region[2,3] consistent with a suggested formula (I)[2]; an analogous formula for the hydrocarbon part of the complex therefore seems unlikely. The spectrum in the CH region would be consistent with an alternative structure involving co-ordinated cyclooctatetraene. There are, however, well defined differences between the spectrum as a whole and these of the cyclooctatetraene complexes $C_8H_8Fe(CO)_3$, $C_8H_8(CuCl)_2$ and $C_8H_8AgNO_3$. Although these differences are most pronounced in the regions of C=C stretching and out-of-plane CH angle deformation vibrations, and might

---

[2]C.D. Nenitzescu (personal communication).

[3]L.J. Bellamy, Infra-red Spectra of Complex Molecules (2nd Edition) Methuen, London, 1958.

in part be explicable in terms of the different extent to which C=C bonds are coordinated to metal atoms, it seems on balance more likely that the structure is a monomeric one.

1960

The complexity of the overall spectrum mentioned above is most evident in the skeletal and CH deformation regions[3], and is not found in those parts of the spectrum which are more readily interpreted in structural terms. The two bands in the CH region, one in the "C=C" region at 1479 cm^{-1} (it is possible, but not likely, that a second band is overlaid by the strong nitrate absorption below 1440 cm^{-1}), and one in the region expected for Ag-C vibrations at 474 cm^{-1}, all point to a structure that is not of great complexity and in which the Ag atom is linked in an equivalent fashion to each of the C=C bonds.

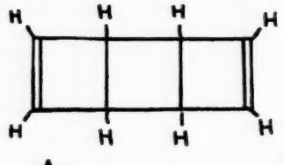
Before proceeding further it is necessary to consider the frequencies of the NO_3^- ion. Silver nitrate itself shows its fundamental infra-red bands at 1350 (V.S.), 807(S) and 738 cm^{-1} (M), the first and last of which correspond to doubly degenerate vibrations[4]. Two very

---

[4] G. Herzberg, Infra-red and Raman Spectra of Polyatomic Molecules. Van Nostrand, New York, 1945.

strong bands at 1385 and 1305 cm^{-1} in the spectrum of the complex correspond to the first of the NO_3^- frequencies and the split degeneracy shows that the ion has probably been reduced in symmetry from D_{3h} to C_{2v} or less. In this situation the ca. 740 cm^{-1} band should also be split in the spectrum of the complex and the symmetrical N-O stretching frequency at ca. 1050 cm^{-1} becomes allowed. We therefore provisionally assign bands to the nitrate ion as indicated in the Table. There remain in the 1600 to 600 cm^{-1} region three strong bands at 1479, 936 and 827 cm^{-1}, three of medium intensity (1176, 1161 and 1042 cm^{-1}) and five weak bands for assignment to the hydrocarbon ligand, although the list may be incomplete because of the regions obscured by NO_3^- absorptions, particularly between 1400 and 1250 cm^{-1}.

The spectroscopic data may now be considered in relation to possible structures for $\left[C_4H_4.Ag\right]^+$ ion. We shall discuss principally the four structures (II) to (V) based on a

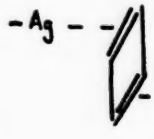


(I)

(II)

(III)

(IV)



(V)

Table 1: Infra-red frequencies of $[C_4H_4.Ag]NO_3$ in the solid state (mulled in nujol, hexachlorobutadiene, and fluorolube)

3053	(W)	CH stretching
2994	(M)	
2304	(W)	NO_3^- combination (1059 + 1305)
1757	(W)	NO_3^- combination (718 + 1059)
1479	(S)	"C=C" stretching
1385	(VS)	NO_3^- (Asymm. NO stretching)
1305	(VS)	
1176	(M)	NO_3^- (Symm. NO stretching)
1161	(M)	
1059	(W)	
1042	(M)	
1006	(W)	
965	(W)	
936	(S)	
859	(W)	NO_3^- (Out-of-plane deformation)
842	(W)	
827	(S)	
814	(S)	
758	(M)	NO_3^- (in-plane deformation)
718	(W)	
641	(W)	
474	(S)	Ag-C stretching

(W) weak, (M) medium, (S) strong, and (VS) very strong bands. The relative intensities only were estimated.

planar C_4H_4 unit. This type of formula accounts readily for the ethylenic type CH frequencies, and for the band at 1479 cm^{-1} which is in a very reasonable position for a C=C group of a 4-membered ring coordinated to a silver atom[5,6]. It is more difficult to account for the latter band, or for the Ag-C frequency of 474 cm^{-1}, on the basis of the tetrahedral C_4H_4 unit suggested by Lipscomb[7]; a higher C=C frequency would be expected for a C_4Ag 5-membered ring.

The structures(II) to (V) require 5, 14, 10 and 7 infra-red active fundamentals respectively in the 1600 500 cm^{-1} region[4] for comparison with six bands of considerable intensity and five weaker ones. Taking the

---

[5] R.C. Lord and F.A. Miller, Applied Spectroscopy 10, 115 (1956).

[6] J. Chatt and L.A. Duncanson, J.Chem.Soc. 2939 (1953); D.B. Powell and N. Sheppard, Spectrochim.Acta. 13, 69 (1958); H.P. Fritz (unpublished work)

[7] W.N. Lipscomb, Tetrahedron Letters No.18, 20 (1959).

1960

spectroscopic evidence at its face value a highly unsymmetrical structure such as (III) seems unlikely (particularly as it would require two C=C frequencies) and (IV) and (V) seem more probable. Strictly speaking (IV) also requires two C=C and Ag-C frequencies, but in this case it would be less surprising if one of each were weak. There are too many bands in the spectrum for the most symmetrical structure (II) to be present in the crystalline state. However it would perhaps be unwise to rule out this structure for a free ion in solution, as some of the spectral complexity may be the result of crystal distortions as for the nitrate ion. In summary, although a dimeric structure containing an ethylenic - type hydrocarbon ligand cannot entirely be ruled out on the basis of the spectroscopic evidence, the infra-red spectrum provides support for a monomeric formulation of $[C_4H_4.Ag]NO_3$ involving an essentially planar hydrocarbon ligand, with structure (V) as most probable on the spectroscopic evidence alone.

We are particularly grateful to Professor C.D. Nenitzescu for samples of $[C_4H_4.Ag]NO_3$. We should also like to thank Dr. G. Schrauzer for samples of cyclooctatetraene complexes, and Dr. L.J. Bellamy for discussions.

Tetrahedron Letters No. 26, pp. 42-44, 1960. Pergamon Press Ltd. Printed in Great Britain

SOME CYCLOPROPENE REARRANGEMENTS

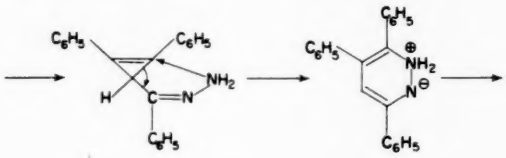
R. Breslow, R. Boikess and M. Battiste

Department of Chemistry, Columbia University, New York

(Received 5 November 1960)

RECENTLY Chandross and Smolinsky reported the rearrangement of triphenylcyclopropenyl azide to triphenyltriazine.[1] As they noted in their paper, we had also observed this interesting reaction, and we wish to report here some other cases in which ring expansions occur by internal attack of a substituent attached to the saturated carbon of a diphenylcyclopropene derivative.

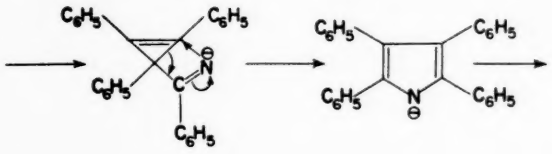
The most closely related example comes from the attempt to prepare the hydrazone of 1,2-diphenyl-3-benzoylcyclopropene. Although an oxime of this compound is easily prepared, reaction of the ketone with hydrazine hydrate in refluxing ethanol led to 3,4,6-triphenyldihydropyridazine, identified by comparison of this compound and its dehydrogenation product with authentic samples.



1 E. Chandross and G. Smolinsky, Tetrahedron Letters, No. 13, 19 (19

1960

A similar rearrangement, in that a nucleophile attacks the double bond and the resulting rearranged anion is resonance stabilized, occurs when triphenylcyclopropenyl cyanide is treated with phenyl lithium. In this case the only product isolated is tetraphenylpyrrole. The reaction is similar to the thermal rearrangement of cyclopropyl imines[2] and ketones[3] to five-membered heterocycles, but in our case it occurs even at -50° C.



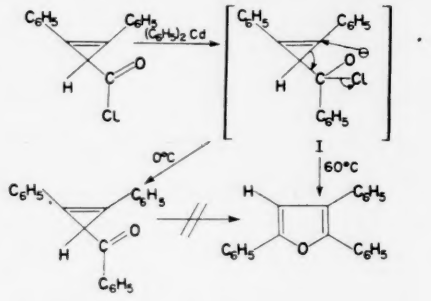
Perhaps the most unusual situation occurs in the reaction of diphenylcyclopropenecarboxylic acid chloride with phenyl cadmium reagent in benzene. Addition of the acid chloride at 0° yields only the expected phenyl ketone, but when the addition is carried out at 60° the only isolable product is 2,3,5-triphenylfuran. Under the latter conditions some tarry materials are also formed, but none of the cyclopropene ketone can be detected. Since the ketone is completely unchanged on treatment with the phenyl cadmium in refluxing benzene (and the acid chloride is thermally stable) we feel that the results can be explained only if the intermediate adduct (I) rearranges during the loss of chloride ion. This

---

2 J. Cloke, J. Am. Chem. Soc., 51, 1174 (1929).

3 C. Wilson, ibid., 69, 3002 (1947).

reaction thus demonstrates the presence of a discreet intermediate such as (I) in a Grignard-type reaction.



1960

Tetrahedron Letters No. 27, pp. 1-4, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

HYDRIDE HYPERCONJUGATION IN 1(3)-METHYLAZULENES

E. C. Kirby and D. H. Reid

Department of Chemistry, The University, St. Andrews,

Fife, Scotland

(Received 10 November 1960)

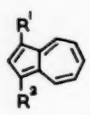
AN outstanding feature of the chemistry of azulene (I), dependent upon its considerable polarization and ready polarizability is the comparatively high degree to which electronic interaction prevails between substituents and the π-electron system of the nucleus.[1,2,3] This is especially reflected in the abnormal polarization of multiple bonds attached to, and conjugated with, the nucleus at $C_{(1)}$ [or $C_{(3)}$]. Consideration of these facts suggested that the methyl group of 1(3)-methylazulenes may interact with the nucleus to an important degree by hydride hyperconjugation. Polar structures [exemplified by (IIb) and (IIc) in the case of 1-methylazulene (II)] should then contribute significantly to the ground state of 1(3)-methylazulenes, with consequent lengthening of the C-H bonds of the 1(3)-methyl group, and in a suitable environment hydrogen might be capable of ready removal from the methyl group as hydride ion. We present now results of experiments on

---

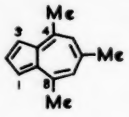
1 D.H. Reid, Azulene and Related Substances p. 69. Special Publication No. 12 of the Chemical Society, London (1958).

2 E.C. Kirby and D.H. Reid, J. Chem. Soc. 494 (1960).

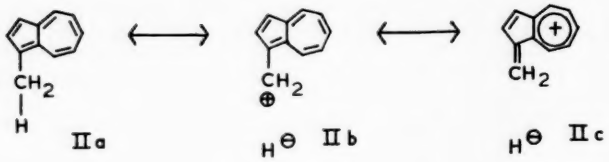
3 D.H. Reid, W.H. Stafford and W.L. Stafford, J. Chem. Soc. 1118 (1958).



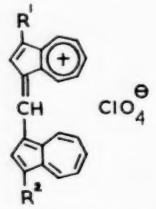
I $R^1 = R^2 = H$
II $R^1 = Me$, $R^2 = H$
III $R^1 = Ph_3C$, $R^2 = H$
IV $R^1 = R^2 = Ph_3C$



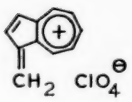
V



IIa ⟷ IIb ⟷ IIc

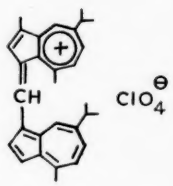


VI $R^1 = Me$, $R^2 = H$
VII $R^1 = R^2 = Me$

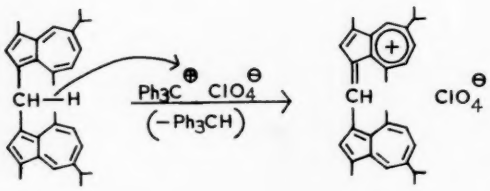


VIII

IX



X



XI XII

the reactions of azulenes with triphenylmethyl perchlorate, which are satisfactorily interpreted on the basis of these ideas.

Azulene (I) underwent electrophilic substitution by triphenylmethyl perchlorate in boiling acetic acid to give a mixture of the dimorphic 1-triphenylmethylazulene (III) (Found: C, 93.6; H, 6.2. $C_{29}H_{22}$ requires C, 93.9; H, 6.1%), blue prisms which melt at 110-120° with subsequent resolidification (>135°) to blue needles, m.p. 175-177° [λ_{max} (in benzene) 602 mμ; log ε 2.49], and 1,3-bis triphenylmethylazulene (IV) (Found: C, 94.1; H, 5.9. $C_{48}H_{36}$ requires C, 94.3; H, 5.5%), blue crystals, m.p. 289-291° [λ_{max} (in benzene) 622 mμ; log ε 2.54]. Notably, 4,6,8-trimethylazulene (V) failed to react. The 4- and 8-methyl substituents evidently screen effectively the 3- and 1-positions of the nucleus against electrophilic attack by the bulky triphenylmethyl cation, and are themselves unattacked.

In contrast, triphenylmethyl perchlorate reacted with an excess (400%) of 1-methylazulene (II) under identical conditions to give in 80% yield a dye-salt, green needles (from acetonitrile), m.p. 350°(decomp.) (on block preheated to $\not<$350°) [λ_{max} (in acetic acid) 652 mμ; log ε 5.02]. Triphenylmethane was formed concomitantly, being isolated in comparable yield. The dye-salt (Found: C, 70.0; H, 4.9; Cl, 9.1%), at first believed to be 1-(azulen-1-yl methylene)-3-methylazulenium perchlorate (VI), is now known to be identical with 1-(3-methylazulen-1-yl)methylene-3-methylazulenium perchlorate (VII)[4] ($C_{23}H_{19}ClO_4$ requires C, 70.0; H, 4.9; Cl, 9.0%) on the basis of a comparison of the visible and infra-red spectra and X-ray powder diagrams of the three salts. These results demonstrate that in the primary step the triphenylmethyl cation attacks the 1-methyl substituent, abstracting

---

[4] E.C. Kirby and D.H. Reid, J. Chem. Soc. In press.

a hydride ion with formation of the reactive methyleneazulenium perchlorate (VIII) which, in an as yet unclarified manner, reacts further with the excess of 1-methylazulene to give eventually (VII).

Guaiazulene (IX) with triphenylmethyl perchlorate likewise gave a dye-salt (48% yield), green needles (from acetic acid), m.p. 260-262.5° (block preheated to 250°) [λ_{max} (in acetic acid) 632 mμ; log ε 5.03], which is believed to possess structure (X) (Found: C, 73.2; H, 6.7; Cl, 7.4. $C_{30}H_{33}ClO_4$ requires C, 73.1; H, 6.8; Cl, 7.2%). Triphenylmethane (71%) was isolated from the mother liquors.

3,3'-Diguaiazulenylmethane (XI)[5] reacted similarly, as depicted, to give a complex mixture from which 5-isopropyl-1-(5-isopropyl-3,8-dimethylazulen-1-yl)methylene-3,8-dimethylazulenium perchlorate (XII) was isolated in low yield, black crystals (from acetic acid), m.p. 243-248° (decomp.), identical (m.p. mixed m.p., and visible spectrum) with an authentic specimen[6] prepared by condensation of guaiazulene with 3-ethoxymethyleneguaiazulenium perchlorate. Triphenylmethane was isolated from the mother liquors.

Full details of these and related experiments will be published later. Thanks are expressed to the Department of Scientific and Industrial Research for the award of a Research Studentship (to E.C.K.), the Royal Society for a Research Grant, and Dr. D. G. Watson for comparisons of the X-ray powder diagrams.

---

[5] H. Arnold and K. Pahls, Ber. 89, 121 (1956).

[6] E.C. Kirby and D.H. Reid. Unpublished results.

Tetrahedron Letters No. 27, pp. 5-8, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

SYNTHESE VON SOLANUM-ALKALOIDEN AUS 3β-ACETOXY-5α-PREGN-16-EN-20-ON*

K. Schreiber und G. Adam

Deutsche Akademie der Landwirtschaftswissenschaften zu Berlin,

Forschungsstelle für Biologie und Bekämpfung der Nematoden,

Mühlhausen/Thüringen

(Received 14 November 1960)

AUS 3β-Acetoxy-5α-pregn-16-en-20-on synthetisierten wir nach bekannten Verfahren über das 16β,17α-Bromhydrin[1] 3β,16β-Diacetoxy-5α-pregnan-20-on (I) vom Fp. 193-195° und $[\alpha]_D^{22}$ + 16.8°**[2] (ber. für $C_{25}H_{38}O_5$ (418.6): 71.74% C, 9.15% H; gef. 72.01% C, 9.18% H). Umsetzung von **I** mit 2-Lithio-5-methyl-pyridin (aus 2-Brom-5-methyl-pyridin[3] und Phenyl-lithium) bei -35 bis -45° in abs. Äther/Benzol[4] führte in 55-proz. Ausbeute zu einem

---

* Solanum-Alkaloide. XIV. Mitteil. - XIII. Mitteil.: K. Schreiber und G. Adam, Experientia im Druck.

** Alle Fp. korrigiert; alle Drehwerte in Chloroform, falls nicht anders angegebenl die Mikroanalysen wurden von Herrn Dr. A. Schoeller, Kronach/Obfr., ausgeführt. Herrn Dr. K. Heller, Wissenschaftliche Laboratorien des VEB Jenapharm, Jena, danken wir für Aufnahme und Diskussion der IR-Spektren.

1 S.G. Levine und M.E. Wall, J.Amer.Chem.Soc. 81, 2829 (1959).

2 R. Neher, Ch. Meystre und A. Wettstein, Helv.Chim.Acta 42, 132 (1959). Diese Autoren fanden für Verbindung I Fp. 174°, $[\alpha]_D^{28}$ + 53.0° (Chloroform/Methanol 1:1).

3 F.H. Case, J.Amer.Chem.Soc. 68, 2574 (1946).

4 Zur Methodik vgl. F.C. Uhle, J.Amer.Chem.Soc. 73, 883 (1951); J. Heer und K. Hoffmann, Helv.Chim.Acta 39, 1804, 1814 (1956); U.S. Pat. 2750380 vom 12. 6. 1956.

POCl₃/Py
II R=H
III R=Ac
Ac₂O/Py
H₂/PtO₂
5% meth. KOH
Va R=~~ H,25D
Vb R= —— H,25L
Vc R= —— H,25L.
I
IV
VI
VII

einheitlichen 3β,16β,20-Trihydroxy-20-(5'-methyl-pyridyl-2')-5α-pregnan (II) vom Fp. 326-329° und $[\alpha]_D^{18}$ + 64.6° in Pyridin (ber. für $C_{27}H_{41}NO_3$ (427.6): 75.83% C, 9.66% H, 3.28% N; gef. 76.24% C, 9.53% H, 3.27% N). II gab mit Acetanhydrid/Pyridin (20 Stdn. bei Raumtemp.) in 81-proz.Ausbeute ein 3,16-Diacetat III vom Doppel-Fp. 186-187° und 210° sowie $[\alpha]_D^{21}$ + 16.6° (ber. für $C_{31}H_{45}NO_5$(511.7): 72.76% C, 8.86% H, 2.74% N; gef. 72.78% C, 8.94% H, 2.81% N). Erhitzen mit Phosphoroxychlorid/Pyridin (3 Stdn. am Rückfluß) lieferte nach Chromatographie an Aluminiummoxyd in 56-proz. Ausbeute ein Dehydratisierungsprodukt vom Doppel-Fp. 142-144° und 154-155° sowie $[\alpha]_D^{25}$ + 28.7° (ber. für $C_{31}H_{43}NO_4$ (493.7): 75.42% C, 8.78% H, 2.84% N; gef. 75.40% C, 8.66% H, 2.80% N), dem auf Grund analoger Umsetzungen[5] die Struktur IV zukommen dürfte. Die katalytische Hydrierung von IV (PtO_2/Eisessig) verlief weitgehend stereospezifisch und ergab nach Verseifung des Hydrierproduktes (5-proz. methanol. KOH, 2,5 Stdn. am Rückfluß) als Hauptprodukt Tetrahydro-solasodin (Dihydro-5α-solasodan-3β-ol, Va) mit 25D-Konfiguration, das sich in seinen Eigenschaften (Fp. 290-295°, Misch-Fp. ohne Depression, $[\alpha]_D^{20}$ - 2,4°, IR-Spektrum und papierchrom. Verhalten) mit authent. Tetrahydro-solasodin[6] als identisch erwies. Daneben wurden papierchromatographisch geringe Mengen der beiden an C_{22} isomeren Dihydro-tomatidine A und B (Vb und c) mit 25L-Konfiguration[7] nachgewiesen (Papierchromatographie: Benzol/Methanol/Wasser 2:1:1, obere Phase; Papier Schleicher & Schüll 2045a;

---

[5] B. Koechlin und T. Reichstein, Helv.Chim.Acta 27, 549 (1944); J. Heer und K. Hoffmann, Helv.Chim.Acta 39, 1814 (1956); E.D. Bergmann, M. Rabinovitz und Z.H. Levinson, J.Amer.Chem.Soc. 81, 1239 (1959).

[6] H. Rochelmeyer, Arch.Pharm.Ber.Dtsch.Pharm.Ges. 277, 329 (1939); L.H. Briggs und I. O'Shea, J.Chem.Soc. 1654 (1952).

[7] Y. Sato und H.G. Latham, J.Amer.Chem.Soc. 78, 3146 (1956).

40stdg. absteigende und durchlaufende Entwicklung bei 16-18°; Sichtbarmachung mit Jod/Kaliumjodid-Lösung; Tetrahydro-solasodin $R_{St.}$ = 0.57, Dihydro-tomatidin B $R_{St.}$ = 0.21, bezogen auf Dihydro-tomatidin A $R_{St.}$ = 1.00).

Aus diesen Ring E-offenen Dihydro-Verbindungen Va-c können sowohl die Spiroaminoketal-Alkaloide Soladulcidin (5α-Solasodan-3β-ol, VI) bzw. Tomatidin (5α-Tomatidan-3β-ol)[8] als auch die tertiären Solanum-Basen vom Typ des Demissidins (5α-Solanidan-3β-ol, VII)[7,9] erhalten werden.

Da 3β-Acetoxy-5α-pregn-16-en-20-on bereits totalsynthetisch zugänglich ist,[10] stellt die durchgeführte Reaktionsfolge einen Weg zur Totalsynthese der genannten Solanum-Alkaloide dar.[11]

---

[8] K. Schreiber und G. Adam, Experientia im Druck.

[9] R. Kuhn, I. Löw und H. Trischmann, Angew.Chem. 64, 397 (1952); Y. Sato, H.G. Latham und E. Mosettig, J.Org.Chem. 22, 1496 (1957).

[10] H. Lettre, H.H. Inhoffen und R. Tschesche, Über Sterine, Gallensäuren und verwandte Naturstoffe Bd. 2. Ferdinand Enke Verlag, Stuttgart (1959); V. Schwarz, V. Cerny und F. Sorm, Coll.Czech.Chem.Comm. 23, 940 (1958).

[11] Vgl. auch Y. Mazur und F. Sondheimer, J.Amer.Chem.Soc. 81, 3161 (1959).

Tetrahedron Letters No. 27, pp. 9-11, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

ABSOLUTE KONFIGURATION DES STEROIDALKALOIDS SOLANOCAPSIN AN C-25*

K. Schreiber und H. Ripperger

Deutsche Akademie der Landwirtschaftswissenschaften zu Berlin,

Forschungsstelle für Biologie und Bekämpfung der Nematoden,

Mühlhausen/Thüringen

(Received 14 November 1960)

DAS in Solanum pseudocapsicum L., S. capsicastrum Link und S. hendersonii hort. vorkommende Steroidalkaloid Solanocapsin ließ sich, wie bereits mitgeteilt,[1] über N,N'-Diacetyl-solanocapsin und N,N'-Diacetyl-3β-amino-22, 26-imino-16β,23-oxido-5α,25ξ-cholest-22-en in die Verbindung I überführen. Nach Spaltung von I mit 14-proz. wäßrig-äthanolischer Salzsäure konnte neben 3β-Amino-16β-hydroxy-5α-bis-22,23-nor-cholansäure-lacton (3-Desoxy-3β-amino-tigogenin-lacton, II)[1] in 24-proz. Ausbeute (-)-4-Amino-3-methyl-buttersäure (III) vom Fp 186-188° und $[\alpha]_D^{25}$ -9.4° (Wasser) isoliert werden (ber. für $C_5H_{11}NO_2$ (117.2): C 51.26%, H 9.46%, N 11.96%; gef. C 51.26%, H 9.36%, N 11.96%).** Ein papierchromatografischer Vergleich mit synthetischer

---

* Solanum-Alkaloide. XV. Mitteil. - XIV. Mitteil.: K. Schreiber und G. Adam, Tetrahedron Letters No. 27, 5 (1960).

** Die Mikroanalysen wurden von Herrn Dr. A. Schoeller, Kronach/Obfr. ausgeführt.

1 K. Schreiber und H. Ripperger, Experientia im Druck.

2 Von J.B. Cloke, E. Stehr, T.R. Steadman und L.C. Westcott, J.Amer. Chem.Soc. 67, 1587 (1945) wird Fp 174° angegeben.

DL-4-Amino-3-methyl-buttersäure vom Fp 193°[2] (ber. für $C_5H_{11}NO_2$ (117.2): C 51.26%, H 9.46%, N 11.96%; gef. C 50.92%, H 9.00%, N 11.64%), dargestellt aus 3-Methyl-glutarsäure-monoamid durch Hofmannschen Abbau,[3] zeigte keine Unterschiede.

Aus der Aminosäure III ließ sich durch Desaminierung mit Natriumnitrit/25-proz. Essigsäure die als Lacton isolierte, jedoch nicht näher untersuchte 4-Hydroxy-3-methyl-buttersäure (IV) darstellen. Anschließende Oxydation mit Kaliumpermanganat in alkalischem Milieu führte in 12-proz. Ausbeute (bezogen auf III) zu D-(+)-Methyl-bernsteinsäure (V) vom Fp 112-114° und $[\alpha]_D^{19}$ + 16.2° (absol. Äthanol). Misch-Fp mit authent. D-(+)-Methyl-bernsteinsäure vom Fp 112-114° und $[\alpha]_D^{24}$ + 17.1° in absol. Äthanol (Lit.:[4] Fp 115°, $[\alpha]_D^{20}$ + 16.88° in absol. Äthanol) ohne Depression. Die IR-Spektren beider Substanzen erwiesen sich als identisch.*

Durch die Bestimmung der absoluten Konfiguration der Aminosäure III als D-(-)-4-Amino-3-methyl-buttersäure ist gleichzeitig die absolute Konfiguration von Solanocapsin and C-25 ermittelt; die C-27-Methyl-Gruppe besitzt äquatoriale Konformation. Solanocapsin ist somit 3β-Amino-22,26-imino-16β,23-oxido-5α,22α,23β,25α-cholestan-23-ol (3β-Amino-22,26-imino-16β, 23-oxido-5α,22R,23S,25R-cholestan-23-ol,[5] VI) und gehört wie beispielsweise

---

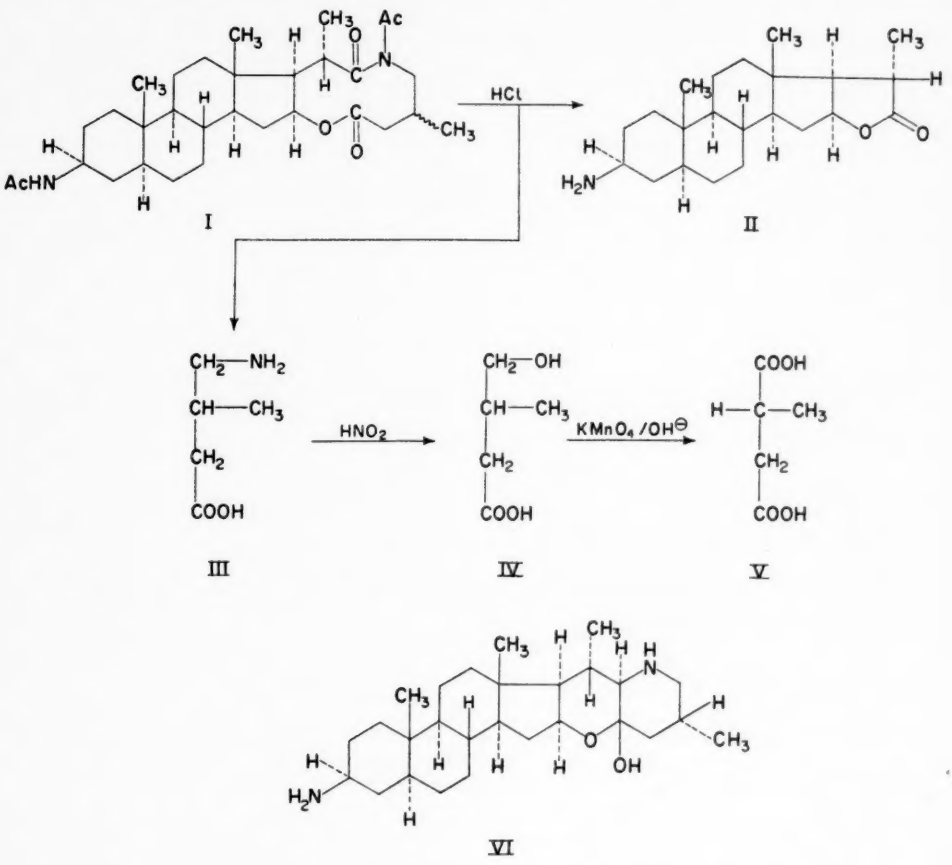
* Herrn Dr. K. Heller, Wissenschaftliche Laboratorien des VEB Jenapharm, Jena, danken wir für Aufnahme und Diskussion der IR-Spektren.

3 S.S.G. Sircar, J.Indian Chem.Soc. 5, 549 (1928).

4 E. Berner und R. Leonardsen, Liebigs Ann. 538, 1 (1939). Zur absoluten Konfiguration der Methyl-bernsteinsäuren vgl. A. Fredga, The Svedberg 1884 30/8 p. 261 Uppsala (1944); A. Fredga und E. Leskinen, Ark.Kem., Mineralog., Geol. (Ser. B) 19, No. 1 (1944); K. Freudenberg und W. Hohmann, Liebigs Ann. 584, 54 (1953).

5 Zur Bezeichnung der absoluten Konfiguration durch Rund S vgl. R.S. Cahn, C.K. Ingold und V. Prelog, Experientia 12, 81 (1956).

1960



Solasodin[6] und Diosgenin[7] zu den Steroiden der 25D-Reihe.

---

[6] Vgl. K. Schreiber, Abh.Dtsch.Akad.Wiss.Berlin, Kl. f. Chem.,Geol. u. Biol. 1956, No. 7, 143 (1957).

[7] V.H.T. James, J.Chem.Soc. 637 (1955).

Tetrahedron Letters No. 27, pp. 13-16, 1960. Pergamon Press Ltd. Printed in Great Britain

A NEW TRITERPENE CARBOXYLIC ACID FROM TERMINALIA TOMENTOSA WIGHT ET ARN.

L. Ramachandra Row and G. S. R. Subba Rao

Department of Chemistry, Andhra University, Waltair, India

(Received 7 June 1960; in revised form 18 November 1960)

RECENT investigations of King et al. on T. arjuna Bedd.[1] and T. ivorensis[2,3] revealed the presence of two new triterpene carboxylic acids, arjunolic and terminolic acids (I and II).

Among the commercial Indian Terminalia species,[4] T. tomentosa Wight et Arn. is a frequent substitute for teak wood. Although it is credited with fungal resistance, it it not resistant towards white ants. The wood is dark brown, heavy and difficult to work with. Solvent extraction with petroleum ether, ether and acetone was carried out and the extracts fractionated. From the petroleum ether extract, β-sitosterol (m.p. 136-137°; $[\alpha]_D^{31^\circ}$ -35°; acetate, m.p. 126-127°) and oleanolic acid (m.p. 306-309°; $[\alpha]_D^{31^\circ}$ +76°; methyl ester, m.p. 200-202°; acetate, m.p. 260-261°) were isolated. The ether extract could be separated into a new triterpene carboxylic acid (m.p. 328-330°) and a small quantity of a neutral triterpenoid which was not examined any more.

---

1 F.E. King, T.J. King and J.M. Ross, J.Chem.Soc. 3995 (1954).

2 F.E. King, T.J. King and J.M. Ross, J.Chem.Soc. 1333 (1955).

3 F.E. King and T.J. King, J.Chem.Soc. 4469 (1956).

4 R.S. Pearson and H.P. Brown, Commercial Timbers of India Vol. 1, Government of India, Central Publication Branch, Calcutta (1932).

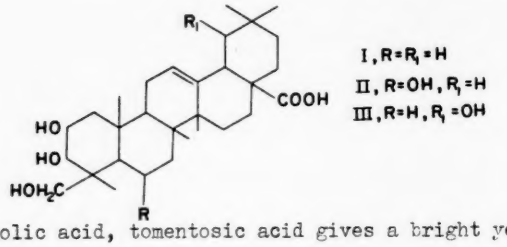
1960

The acetone extract furnished a sparingly soluble colourless solid (yield, 1.5%) identified as arjunolic acid (m.p. 332-334°; $[\alpha]_D^{31°}$ +63°; methyl ester, m.p. 209-211°; $[\alpha]_D^{31°}$ +62°; bromo lactone, m.p. 232-234°; $[\alpha]_D^{31°}$ +53°; bromo lactone triacetate, m.p. 182-183°; $[\alpha]_D^{31°}$ +50°). Our identification of this acid was kindly confirmed by Dr. E. Morgan of British Celanese Ltd. by a mixed melting point and infra-red spectral comparison with an authentic sample of arjunolic acid.

The triterpene carboxylic acid from the ether extract has a molecular formula, $C_{30}H_{48}O_6$. It contained a carboxyl and four hydroxyl groups. It is isomeric with terminolic acid but not identical with it (Table 1) and is therefore named tomentosic acid. The new acid dissolves in conc H_2SO_4 to give a colourless solution initially changing to orange pink in course of time.

Table 1

	Tomentosic acid			Terminolic acid II[2,3]	
Found	Reqd. for	m.p.	$[\alpha]_D^{31°}$	m.p.	$[\alpha]_D$
Acid	$C_{30}H_{48}O_6$				
C, 71.8	C, 71.4	328-330°	+ 64°	332-334°	+ 42°
H, 9.3	H, 9.5				
Methyl ester	$C_{31}H_{50}O_6$				
C, 71.1	C, 71.8	221-222°	+ 72°	165-168°	+ 40°
H, 9.9	H, 9.6				
OMe, 6.3	1-OMe, 6.2				
Epoxide of ester	$C_{31}H_{50}O_7$				
C, 69.2	C, 69.6	158-160°		175°	+ 7.7°
H, 9.5	H, 9.3				
Bromolactone	$C_{30}H_{47}O_6Br$				
C, 61.5	C, 61.7	234-236°	+ 45°	232°	+ 32°
H, 8.8	H, 8.1				
Anhydrolactone triacetate	$C_{36}H_{52}O_8$				
C, 70.0	C, 70.6	250-254°	+ 1.8°	211-212°	+ 8°
H, 8.9	H, 8.6				



I, R=R1=H
II, R=OH, R1=H
III, R=H, R1=OH

Like terminolic acid, tomentosic acid gives a bright yellow colour with tetranitro methane. The infra-red spectrum[5] of the methyl tomentosate revealed characteristic absorption at 11.7 mμ (851 cm^{-1}) and 12.2 mμ (922 cm^{-1}) indicating a trisubstituted double bond.[6]

Tomentosic acid yields both a triacetate and a tetra acetate; but the acetyl derivatives are very difficult to purify and the melting points were never sharp. The methyl ester furnished an isopropylidine derivative (m.p. 168-170°; $[\alpha]_D^{31}$ +68°; Found: C, 73.5; H, 9.9; $C_{34}H_{54}O_6$ requires C, 73.1; H, 9.7) suggesting a 1:3 diol system in the molecule. Copper pyrolysis at 270-290° gave rise to small quantities of formaldehyde identified as dimedone derivative, thus confirming the presence of 3: 23 diol system in the molecule.[7]

Further information regarding the disposition of the hydroxyls in the molecule was secured through periodate and lead tetra acetate oxidations of the methyl ester. From the ease with which periodate was consumed (0.99 mole) and the time (14 hr) required for complete oxidation with lead tetra acetate, it is presumed that the molecule must contain α:β glycol.[8] But the isoproylidine derivative was inert to periodate; the remaining two hydroxyls are, therefore, not in a glycol system. From the foregoing, the presence of

---

5 I.R. spectra reported in this paper were taken in $CHCl_3$ solution on a Cambridge instriument at the National Physical Laboratory, Delhi.

6 A. Meyer, O. Jeger and L. Ruzicka, Helv.Chim.Acta 33, 687 (1950).

7 K. Tsuda and S. Kitagawa, Ber. 71, 1604 (1938).

8 Carl Djerassi, D.B. Thomas, A.L. Livingston and C. Ray Thompson, J.Amer.Chem.Soc. 79, 5292 (1957).

1960

2α: 3β: 23 (24) -trihydroxy system may be inferred as in arjunolic and terminolic acids.

The following reactions confirm that tomentosic acid belongs to oleanolic acid series of β-amyrin group. (1) The methyl ester is stable to alkali. (2) Tomentosic acid readily furnished a stable bromolactone with bromine in acetic acid.[9] (3) The tetra acetyl methyl tomentosate suffered oxidation with selenium dioxide (1 mole in acetic acid) to give a diene having characteristic triple U.V. absorption maxima (λ_{max} 243, 251, 260 mμ; log ε 4.21, 4.31 4.10).[10] (4) Finally, methyl tomentosate was converted into methyl arjunolate by the following sequence of reactions. 2-Acetyl 3:23 isopropylidine methyl tomentosate was oxidized with pyridine-Cr_2O_3 and the resulting ketone (m.p.204-205°) was reduced by Wolff - Kishner method as modified by Barton et al.[11] Removal of the acetyl and isopropylidine groups followed by methylation with diazomethane furnished methyl arjunolate (m.p. 205-207°) undepressed by an authentic sample.

Tomentosic acid undergoes facile lactonization with 50% HBr - acetic acid to give an anhydrolactone diacetate (m.p. 233-235°; $[\alpha]_D^{31°}$ -20°; Found: C, 71.6; H, 8.8; $C_{34}H_{50}O_7$ requires C, 71.6; H, 8.6). Although, the anhydrolactone diacetate or its derivatives did not develop any colouration with tetra nitromethane, it showed a prominent Infra-red absorption for a trisubstituted double bond at 11.6 mμ (861 cm^{-1}) and 12.1 mμ (829 cm^{-1}). Such facile dehydration to produce a trisubstituted double bond may be expected with hydroxyls at 6, 11 and 19 positions only. As tomentosic acid

---

9 O. Jeger, Fortschr.Chem.Org.Naturstoff. 7, 1 (1950).

10 D.H.R. Barton and N.J. Holness, J.Chem.Soc. 78, (1952).

11 D.H.R. Barton, D.A.J. Ives and B.R. Thomas, J.Chem.Soc. 2056 (1955).

is not identical with terminolic acid or its epimer, the 6th position for the fourth hydroxyl is improbable. The 11th position is also excluded since the anhydrolactone triacetate could not be oxidized by pyridine - Cr_2O_3.

Dehydration of triacetyl methyl tomentosate using pyridine - $POCl_3$, benzene - P_2O_5 or selenium dioxide gave rise to a dehydro derivative which was deacetylated and subjected to isomerization with $CHCl_3$ - HCl. The isomeric dehydro tomentosate was not, however, identical with methyl dehydro arjunolate. The methyl dehydrotomentosate (m.p. 198-200°) and its isomer (m.p. 228-230°) gave prominent yellow colouration with tetra nitromethane and possessed a single peak of low intensity at 250 mμ in their U.V. absorption spectra. These reactions seem to exclude the 19th position for the fourth hydroxyl (Fig. III). Tomentosic acid may, therefore, be represented tentatively by 2α : 3β : 23(24): X: tetrahydroxy-olean-12-ene-28-oic acid.

Acknowledgements - Our grateful thanks are due to Prof. F. E. King F.R.S. and to Dr. E. Morgan for confirming our identification of arjunolic acid, to the Director, National Physical Laboratory, Delhi, for the I.R. spectral data and to Prof. T. R. Seshadri F.R.S., Delhi University, Delhi, for U.V. absorption data. We are also grateful to the Council of Scientific and Industrial Research, Delhi, for financial assistance.

Tetrahedron Letters No. 27, pp. 17-20, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

SUBSTITUENT EFFECTS IN THE CHARGE-RESONANCE SPECTRA OF 1,1-DINITROALKANE ANIONS

Mortimer J. Kamlet and Donald J. Glover

Organic Chemistry Division, U. S. Naval Ordnance Laboratory
White Oak, Silver Spring, Maryland, U. S. A.

(Received 28 October 1960; in revised form 29 November 1960)

BALASUBRAMANIAN and Rao[1] have recently reported that frequencies of absorption maxima for the $n \rightarrow \pi^*$ transition of aliphatic nitro compounds are related linearly to Taft's σ^* if a treatment similar to that of Taft and Lewis[2] is applied to account for C-H and C-C hyperconjugation. We wish now to record a linear λ_{max} - σ^* relationship for the primary bands in the charge-resonance spectra of 1,1-dinitroalkane anions, $R\text{-}C(NO_2)_2^-$, a series in which the non-conjugating substituent R has a pronounced inductive influence on the position of the maximum.

Spectra were determined using the potassium salts in 3-5 x 10^{-5} molar concentrations in dilute aqueous alkali and previously described precautions were taken in carrying out all measurements[3]. Absorption maxima for a number of such compounds for which σ^* of R was available or could be deduced are listed in Table I. Extinction coefficients were in the order of 15-20,000 and all spectra showed minima with ε = 1,000 or less in the

---

[1] A. Balasubramanian and C. N. R. Rao, Chem. and Ind. 1025 (1960).

[2] R. W. Taft, Jr. and I. C. Lewis, Tetrahedron 5, 210 (1959).

[3] M. J. Kamlet and L. A. Kaplan, J. Org. Chem. 22, 576 (1957).

280-300 mμ region, so that complications due to band overlap had negligible influence on the positions of λ_{max}.

TABLE I

No.	$R\text{-}C(NO_2)_2^-$, R =	σ^{*} [h]	λ_{max}, mμ	Ref.
XXXV	$t\text{-}C_4H_9CH_2$	-0.165	384	a
XXXIV	$i\text{-}C_4H_9$	-0.130	384	a
V	$n\text{-}C_4H_9$	-0.125	382 (384)	b (a)
III	C_2H_5	-0.100	382 (383)	b (a)
II	CH_3	0.000	381.5 (381)	b (c)
XI	$CH_3COCH_2CH_2$	+0.214[d]	379	b
VII	$(CH_3)_2NCH_2$	+0.22[e]	369.5	b
X	$CH_3OOCCH_2CH_2$	+0.255[f]	379	b
XXIX	$NO_2CH_2CH_2$	+0.50	374	b
XXXVI	$CH_3CH_2OCH_2$	+0.52[g]	365	b
VIII	$HOCH_2$	+0.555	365	b
IX	C_6H_5	+0.600	373	b
VI	$N{\equiv}CCH_2$	+1.300	362.5	b
XXIII	$(CH_3)_3\overset{+}{N}CH_2$	+1.90	352	c

[a] Private communication, Dr. H. Shechter, Ohio State University.

[b] Spectra determined in present investigation.

[c] L. Zeldin and H. Shechter, J. Amer. Chem. Soc. 79, 4708 (1957).

[d] Estimated by dividing value for CH_3COCH_2 by 2.8.

[e] R. W. Taft and I. C. Lewis, J. Amer. Chem. Soc. 80, 2436 (1958).

[f] Estimated by dividing the value for C_2H_5OOC by $(2.8)^2$.

[g] Estimated to be same as value for CH_3OCH_2.

[h] R. W. Taft, Jr. in M. S. Newman, Steric Effects in Organic Chemistry. John Wiley and Sons, New York, 1956, Chapter 13.

Of the fourteen dinitroalkane anions, the λ_{max} - σ^* plot (Figure 1) shows eleven conforming with the expression,

$$\lambda_{max} = (381.6 - 15.25\ \sigma^*)\ m\mu, \qquad (1)$$

the average deviation being less than 0.5 mμ. Compounds VII, VIII and XXXVI, the deviants, all show λ_{max} 8-9 mμ lower than the relationship would predict and have in common a pair of non-bonded electrons on the atom beta to the charged carbon. If the expression is modified as follows,

$$\lambda_{max} = (381.6 - 15.25\ \sigma^* - 8.5\ \gamma)\ m\mu, \qquad (2)$$

where γ is 1.0 or 0.0 depending on the presence or absence of non-bonded electrons on the beta atom, all fourteen points fit, the average deviation again being less than 0.5 mμ.

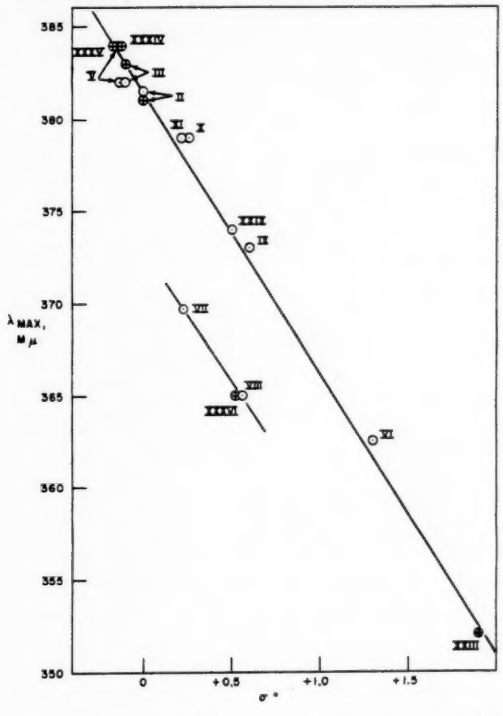


FIG. 1. λ MAX RELATED TO σ*. ⊙ - PRESENT INVESTIGATION. ⊕ - DATA OF SHECHTER

It is noteworthy that λ_{max} shifts hypsochromically with increasing ability of the substituent to delocalize the negative charge by inductive withdrawal of the C-R electron pair in the direction of R. This is in marked contrast with the effect of conjugating electron-withdrawing substituents which generally shift charge-resonance maxima of carbanions bathochromically by providing additional "seats for the resonating charge"[4].

The preparation of the compounds listed in Table I and a more detailed account of the spectra of 1,1-dinitroalkane anions will be presented in future papers. The authors are grateful to Dr. H. Shechter for making available unpublished information and to Drs. L. A. Kaplan, J. C. Dacons and D. V. Sickman for helpful discussions.

---

[4] E. A. Braude in E. A. Braude and F. C. Nachod, Determination of Organic Structures by Physical Methods. Academic Press, New York, 1955, p. 158.

Tetrahedron Letters No. 27, pp. 21-24, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

RATE STUDY ON THE INCORPORATION OF TYROSINE INTO MORPHINE, CODEINE AND THEBAINE

A. R. Battersby and B. J. T. Harper

University of Bristol

(Received 4 November 1960)

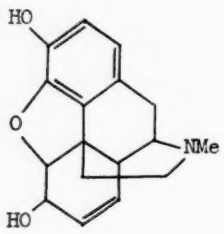
MUCH is now known about the early[1,2] and intermediate[3] stages of morphine biosynthesis and there is considerable interest in the later stages. By feeding [2-^{14}C] tyrosine to Papaver somniferum plants it has been established[1,2] that two molecules of tyrosine are built into morphine (I). Purification of the codeine (II) and thebaine (III) fractions from our feeding experiments has yielded codeine (3.1×10^5 counts per min. per millimole) and thebaine (1.1×10^5 counts per min. per millimole). Morphine from the same plants had an activity of 4.5×10^5 counts per min. per millimole. Tyrosine can thus serve as the precursor of all three alkaloids. This finding allows [2-^{14}C] tyrosine to be used to follow the rate of incorporation of activity into the bases (I), (II), and (III).

---

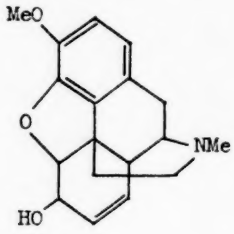
[1] A. R. Battersby and B. J. T. Harper, Chem. & Ind. 363 (1958); A. R. Battersby, R. Binks and D. J. LeCount, Proc. Chem. Soc. 287 (1960).

[2] E. Leete, Chem. & Ind. 977 (1958); E. Leete, J. Amer. Chem. Soc. 81, 3948 (1959).

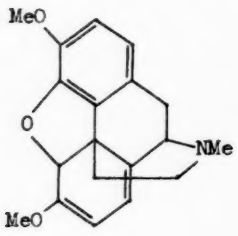
[3] A. R. Battersby and R. Binks, Proc. Chem. Soc. 360 (1960).



I



II



III

Forty five mature poppy plants (1958 season) were fed over 0.5 hr. with [2-^{14}C] tyrosine and at set times after the feeding, groups of five plants were harvested. The alkaloids were extracted and the morphine, codeine and thebaine were isolated by partition chromatography on Whatman No. 1 paper in dioxan, water, 99% formic acid (90, 9.5, 0.5 by volume) for determination of their activities.

We find that the total amounts of alkaloid and the relative amounts of the bases (I), (II) and (III) vary from plant to plant; in addition, these quantities are known to depend upon the stage of development of the

plant.[4] It is therefore necessary to express a result for a given alkaloid as total activity; this gives a measure of the amount of that alkaloid formed from [2-^{14}C] tyrosine which is still present in the plant at the time of harvesting. In order to deal with variations in the total

Time after Feeding	Total Activities x 10^{-3} (counts per 100 sec.)			Ratio Codeine/Morphine	Ratio Thebaine/Morphine
	Morphine	Codeine	Thebaine		
4 hours	7.3	14	33	1.9	4.5
8 hours	24	60	53	2.5	2.2
25 hours	76	77	53	1.0	0.7
2 days	75	91	52	1.2	0.7
3 days	86	36	19	0.4	0.2
5 days	270	55	27	0.2	0.1
8 days	145	29	10	0.2	0.07
11 days	204	25	11	0.1	0.05
14 days	195	21	9	0.1	0.05

incorporation (e.g. apparently more efficient incorporation has occurred in the 5 day experiment) the ratios of activities of the three alkaloids are given. High accuracy is not claimed for these figures, but the experimental error is small compared with the very large changes in activity.

---

[4] R. Miriam and S. Pfeifer, Scienta Pharmaceutica 27, 34 (1959); A. R. Battersby and B. J. T. Harper, unpublished work.

The results show a rapid incorporation of activity into thebaine followed by a rise in the codeine activity and then a steady fall in the activities of these two alkaloids relative to that of morphine. Obviously the simplest interpretation of these facts is that the biosynthetic pathway runs from tyrosine to thebaine which is converted into codeine and that morphine is the end product of the synthesis. Feeding experiments using high activity specifically labelled thebaine are planned.

The above studies are complementary to the recent work of Rapoport et al.[5] who grew poppy plants in ^{14}C-carbon dioxide; they proved that the activities residing in the thebaine, codeine and morphine skeletons (i.e. lacking methyl groups) changed with time as in the experiments above. Rapoport et al. also regard their results as evidence for the pathway thebaine → codeine → morphine.

Grateful acknowledgement is made to Messrs. J. F.Macfarlan and Messrs. T. and H. Smith and to the Rockefeller Foundation for financial support.

[5] H. Rapoport, F. R. Stermitz and D. R. Baker, J. Amer. Chem. Soc. 82, 2765 (1960).

Tetrahedron Letters No. 27, pp. 25-26, 1960. Pergamon Press Ltd. Printed in Great Britain

RAPID INTERMOLECULAR EXCHANGE OF METHYL GROUPS[1]

A. L. Allred and C. R. McCoy

Department of Chemistry, Northwestern University
Evanston, Illinois

(Received 23 November 1960)

The bridge structure[2,3,4] of trimethylaluminum was confirmed recently[5] for the liquid state by the observation of two peaks in the nuclear magnetic resonance (NMR) spectrum of trimethylaluminum dissolved in cyclopentane at -75°C. At room temperature only one NMR peak appears due to either inter- or intramolecular exchange of methyl groups. In this communication, evidence for intermolecular exchange is presented, and calculations of pre-exchange lifetimes and reaction rates are summarized.

Solutions of trimethylaluminum in dimethylcadmium exhibit only one NMR absorption peak. The variation of the chemical

---

[1] This research was supported by grants from the Research Corporation and from the Esso Education Foundation.

[2] A. W. Laubengayer and W. F. Gilliam, J. Am. Chem. Soc. 63, 477 (1941).

[3] K. S. Pitzer and H. S. Gutowsky, J. Am. Chem. Soc. 68, 2204 (1946).

[4] P. H. Lewis and R. E. Rundle, J. Chem. Phys. 21, 986 (1953).

[5] N. Muller and D. E. Pritchard, J. Am. Chem. Soc. 82, 248 (1960).

shift of this peak as a function of concentration, from pure trimethylaluminum to pure dimethylcadmium, is linear. The appearance of only one peak must be the result of rapid intermolecular exchange; magnetic equivalence due to some other process, for instance, formation of complexes, would give a non-linear variation of chemical shift with concentration. From equation 6 of reference 6 and the chemical shifts of three solutions, dimethylcadmium (0.097 M) in benzene, trimethylaluminum (0.062 M) in benzene, and both dimethylcadmium (0.097 M) and trimethylaluminum (0.062 M) in benzene, the upper limit of the average time τ_A before exchange was found to be 0.09 sec.

For solutions of dimethylzinc in dimethylcadmium, the NMR spectrum consists of a single peak the chemical shift of which varies linearly with concentration. Dilution of the dimethylzinc-dimethylcadmium system with inert solvents decreases the average pre-exchange lifetimes of methyl groups and leads to a separation of the nuclear resonance components. Methods discussed in ref. 6 were employed in the calculation of τ_A for 1M dimethylzinc and 1M dimethylcadmium in five solvents: 0.127 sec in cyclohexane, 0.118 sec in benzene, 0.081 sec in ether, 0.087 sec in pyridine, and 0.102 sec in nitrobenzene. The order of the exchange process is approximately 1.7, and the apparent-order rate constants are approximately 10 $(\text{moles/l})^{0.7}$ sec^{-1} for cyclohexane, benzene, pyridine, and nitrobenzene solutions.

All NMR spectra were observed at 40 Mc and at 25°C. A more complete discussion of this research will be presented later.

---

[6] H. S. Gutowsky and C. H. Holm, J. Chem. Phys. 25, 1228 (1956).

Tetrahedron Letters No. 27, pp. 27-30, 1960. Pergamon Press Ltd. Printed in Great Britain

1960

SYNTHESES IN THE CADINANE SERIES:

SYNTHESIS OF (±)-CADINENE DIHYDROCHLORIDE

M. V. R. Koteswara Rao, G. S. Krishna Rao and Sukh Dev*

Organic Chemistry Department, Indian Institute of Science, Bangalore

(Received 28 November 1960)

AN important group of sesquiterpenes belongs to the cadinene group, which is fairly widely distributed in nature. Several dienes (cadinenes, $C_{15}H_{24}$) and mono olefinic t-alcohols (cadinols, $C_{15}H_{26}O$) fall under this category[1,2]. The absolute configuration of compounds of this series has been recently determined[2,3,4] and is shown for the diketone (I), a degradation product of ε-cadinene[5] (II). It appeared to us that the diketone (I) represents the key substance for syntheses in the cadinane group, and this communication describes, first a total synthesis of (±)-4-isopropyl-trans-decalin-1,6-dione (I), and then its conversion into (±)-cadinene dihydrochloride (III).

---

* Present address: Division of Organic Chemistry, National Chemical Laboratory, Poona, India.

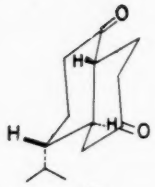
1 D.H.R. Barton, Quart.Rev. 11, 189 (1957).

2 V. Herout and V. Sykora, Tetrahedron 4, 246 (1958).

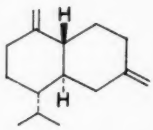
3 F. Hanic, Chem.Listy 52, 165 (1958).

4 V. Sýkora, V. Herout and F. Šorm, Coll.Czech.Chem.Comm. 23, 2181 (1958).

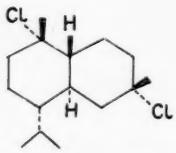
5 V. Herout and F. Santavý, Coll.Czech.Chem.Comm. 19, 118 (1954).



I



II



III

Birch reduction of 4-isopropyl-6-methoxy-tetralone (IV)[6,7] with sodium in liquid ammonia-ethanol gave a highly variable yield (20-70%) of the alcohol (V; b.p. 135-137°/0.6 mm, n_D^{26} 1.5260; no maximum in the 220-300 mμ region; 2:4-dinitrophenyl hydrazone,[8] red needles from acetic acid, m.p. 185°). However, consistent 60-65% yields of V could be obtained by first reducing the tetralone (IV) to 4-isopropyl-6-methoxy-tetralol (VI) by $LiAlH_4$ and then subjecting this crude tetralol to Birch reduction as above. Oxidation of V to the ketone (VII) proved quite elusive; with pyridine-chromic acid[9] or activated manganese dioxide[10] the tetralone (IV) was quantitatively regenerated. Oppenauer oxidation of V with aluminium isopropoxide in acetone-toluene[11] under essentially identical conditions gave either VII (yield 80-90%; b.p. 138-140°/0.6 mm, n_D^{29} 1.5280; λ_{max}^{EtOH} 238 mμ, ε 6900, 241 mμ, ε 7000; dioxime, m.p. 215-217°; bis-2,4-dinitrophenylhydrazone, m.p. 198-199°) or VIII (yield 80-90%; b.p. 130-134°/0.5 mm, n_D^{26} 1.5620; λ_{max}^{EtOH} 339 mμ, ε 9300) or a mixture of both. Attempted separation of VII and VIII on a column of alumina (Basic/I) led to complete isomerization

---

6 G.S. Krishna Rao and Sukh Dev, J.Indian Chem.Soc. 34, 255 (1957).

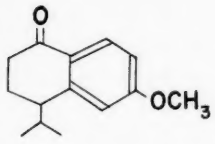
7 J.C. Bardhan and D.N. Mukherji, J.Chem.Soc. 4629 (1956).

8 Derived from the dienone resulting from aqueous acid treatment.

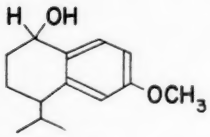
9 G.I. Poos, G.E. Arth, R.E. Beyler and L.H. Sarett, J.Amer.Chem.Soc. 75, 422 (1953).

10 J. Attenburrow, A.F.B. Cameron, J.H. Chapman, R.M. Evans, B.A. Hems, A.B.A. Jansen and T. Walker, J.Chem.Soc. 1094 (1952).

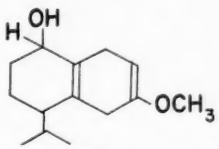
11 A.J. Birch, J.A.K. Quartey and H. Smith, J.Chem.Soc. 1768 (1952).



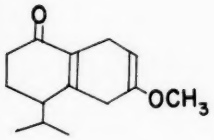
IV



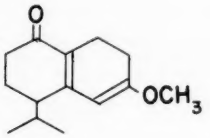
VI



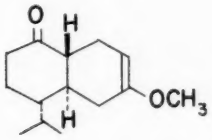
V



VII



VII



IX

to the fully conjugated dienone (VIII). The dienone (VII) was reduced with lithium in liquid ammonia and the resulting crude enol-ether monoketone (IX) treated with dioxane-aqueous hydrochloric acid to furnish a 30% (based on VII) yield of the required (±)-4-isopropyl-trans-decalin-1,6-dione (I). (Colourless needles from benzene-petroleum ether, m.p. 71-71.5°; λ_{max}^{EtOH} 286 mμ, ε 53; dioxime, m.p. 203-204°; bis-2,4-dinitrophenylhydrazone, yellow soft needles from ethanol-chloroform, m.p. 206-207°.) The infra-red spectrum of the diketone is shown in Fig. 1 and has been compared with that of the (-)-diketone of Herout and Santavý,[5] and their complete superimposibility proves that the synthetic diketone has the required stereochemistry.

The synthetic diketone on interaction with excess methyl lithium yielded a glycol as a gum, which on further treatment with hydrochloric acid gas in ether solution readily gave crystalline (±)-cadinene dihydrochloride, m.p.

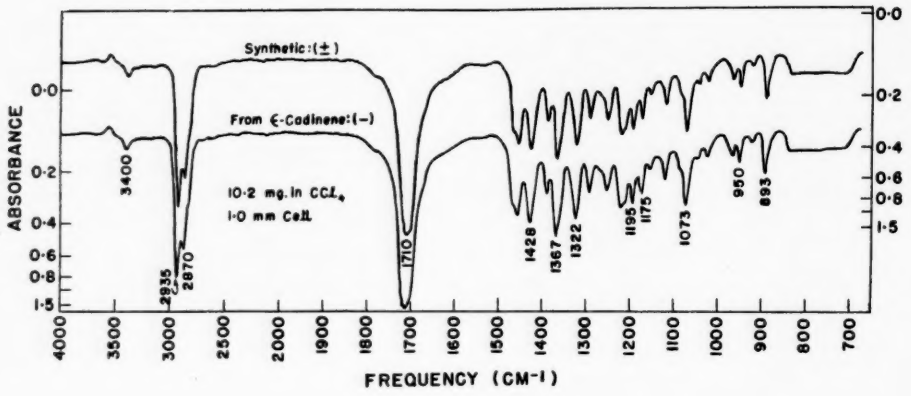


FIG. 1.

105-106°. This compound has been prepared from natural (±)-δ-cadinen,[12,13] and an authentic sample (m.p. 105-106°) did not depress the m.p. of the synthetic material and both exhibited identical infra-red spectra.

Acknowledgments :- The authors wish to place on record their sincere gratitude to Professor F. Sorm and Professor M.D. Sutherland for generous samples of (-)-diketone and (±)-cadinene dihydrochloride respectively. We are also grateful to Professor D.K. Banerjee for evincing keen interest in this investigation.

---

[12] R.O. Hellyer and H.H.G. McKern, Aust.J.Chem. 9, 547 (1956).

[13] R.P. Hildebrand and M.D. Sutherland, Aust.J.Chem. 12, 678 (1959).

Tetrahedron Letters No. 27, pp. 31-36, 1960. Pergamon Press Ltd. Printed in Great Britain

1α,11α-EPOXY-STEROIDS FROM OUABAGENIN BY TRANSANNULAR SUBSTITUTION

G. Volpp[1] and Ch. Tamm

Organisch-chemische Anstalt der Universität Basel; Pharmazeutisch-chemisches Laboratorium SANDOZ Basel, and Department of Chemistry, Harvard University, Cambridge, Mass., U.S.A.

(Received 5 December, 1960)

The cleavage of ouabain (I) with HCl-acetone (ca. 10 days at 0°) according to the classical procedure of Mannich and Siewert[2] yields L-rhamnose and 1,19-isopropyliden-ouabagenin (II)[3]. The removal of the acetone group leading to ouabagenin (III) is effected readily by hydrolysing II with 0.6% (= ca. 0.1 N) H_2SO_4 in aqueous ethanol at 0°[2].

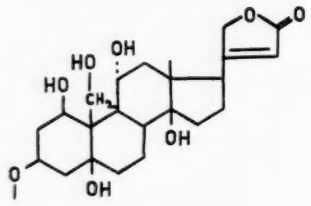
We now have found that II does not yield ouabagenin (III) when refluxed with 0.05 N HCl in aqueous ethanol for 30-60 minutes. Instead two new products are formed, namely a monoanhydro-ouabagenin ($C_{23}H_{32}O_7$) with m.p. 274-275° (capillary tube) or 306-316° (micro hot stage), $[\alpha]_D$ + 46° (methanol) and λ_{max} 217 mμ, log ε 4.17 (ethanol) as the main component and, in about 1/10th the amount, tetranhydro-ouabagenin ($C_{23}H_{26}O_4$) with m.p. 238-240°, [α] + 18° (methanol) and λ_{max} 214.5 mμ,

---

[1] Present address: Department of Chemistry, Harvard University, Cambridge, Mass., U.S.A.

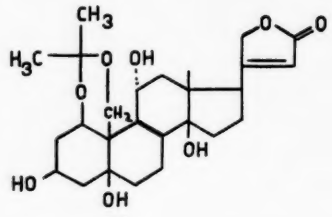
[2] C. Mannich and G. Siewert, Ber.deutsch.chem.Ges. 75, 337 (1942).

[3] Ch. Tamm, Helv.Chim.Acta 38, 147 (1955).

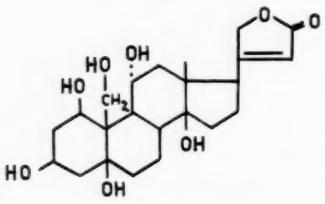


L-Rhamnosyl

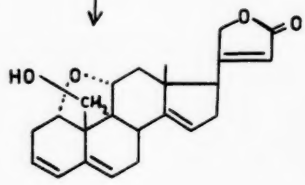
I Ouabain



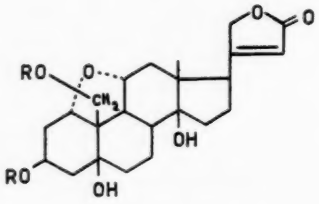
II



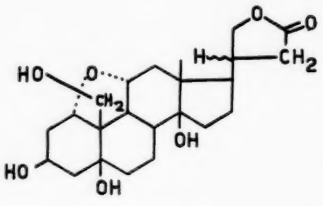
III Ouabagenin



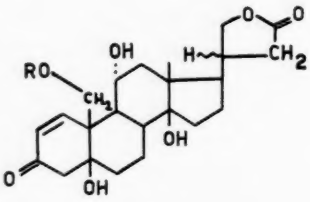
IV



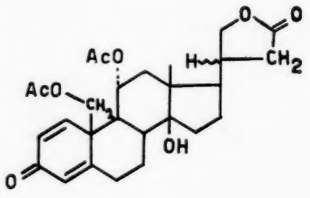
V (R = H) VI (R = Ac)



VII



IX (R = H) X (R = Ac)



XI

1960

log ε 4.42, shoulder at 255-265 mμ, log ε 2.7 (ethanol). The same products are also obtained from ouabagenin (III) itself when hydrolysed under the same conditions. Both structures V and IV are characterized by an 1α,11α-epoxide group and are thus assigned to the monoanhydro and the tetra-anhydro-derivatives respectively on the basis of the following reactions. According to the U.V. spectrum of V the butenolide ring remained unchanged. V gave on treatment with KOH or with K_2CO_3 an iso derivative ($C_{23}H_{32}O_7$, m.p. 267-270°, [α] + 22° (methanol-chloroform (1:1)) indicating the presence of a 14β-hydroxyl in monoanhydro-ouabagenin (V). A chloroform-methanol solution of V gave no yellow colour with tetranitromethane. On catalytic hydrogenation with Pt in acetic acid the dihydro derivative VII ($C_{23}H_{34}O_7$, m.p. 248-252°, $[\alpha]_D$ + 31.5° (methanol), transparent in the U.V.) was obtained. Treatment of V with acetanhydride in pyridine at 60° gave the diacetyl derivative VI ($C_{27}H_{36}O_9$, m.p. 226-230°, $[\alpha]_D$ + 44° (chloroform)).VI was stable against CrO_3 in acetic acid. From these results it is concluded that the dehydration of ouabagenin does not lead to the formation of a C=C bond but gives rise to an ether bridge employing two of the four original hydroxyl groups capable of being acetylated. Since a great number of aglycons of known structure had proved to be stable against an analogous treatment with acid therefore only the five-membered 1α,11α-oxide ring and the four-membered 1β,19-oxide ring remained as sites of location for the oxygen bridge. That the latter could be excluded in favour of the 1α,11β-epoxide ring was adduced by the degradation of monoanhydro-ouabagenin (V) and of the further transformation of the dihydro derivative VII. Selective catalytic dehydrogenation at C-3 of the latter with O_2-Pt[4] in aqueous acetone gave a mixture of the corresponding 3-dehydro derivative VIII (not

isolated) and of the Δ^1-3-ketone IX which both were transformed into the acetylated Δ^1-3-ketone X (amorphous, λ_{max} 232 mμ, log ε 3.95 and λ_{max} 316 mμ, log ε 1.60 (ethanol), I.R. peaks at 5.65 μ, 5.77 μ, 6.20 μ). Thus opening of the oxygen ring took place by base-catalysed rearrangement as observed with β,γ-epoxy-ketones giving γ-hydroxy-α,β-unsaturated ketones[5]. By refluxing with glacial acetic acid the 5-hydroxyl group was removed and the dienone XI was obtained ($C_{27}H_{34}O_8$, m.p. 201-205°, $[\alpha]_D$ + 22° (chloroform), λ_{max} 243 mμ, log ε 4.18 and 330 mμ, log ε 1.61 (ethanol), I.R. peaks at 5.65 μ, 5.76 μ, 6.01 μ, 6.15 μ and 6.23 μ).

Degradation of diacetyl monoanhydro-ouabagenin (VI) with O_3, reductive cleavage of the ozonide and treatment with $KHCO_3$[6] led to the ketol XIII ($C_{21}H_{32}O_7$, m.p. 201-202°, $[\alpha]_D$ + 60° (methanol), λ_{max} 280 mμ, log ε 1.69 (ethanol), I.R. peak at 5.88 μ). After oxidation of VI with $KMnO_4$ in acetone at 22°[7] and methylation of the acid formed with CH_2N_2 and reacetylation amorphous methyl etianate XII was obtained. The two tertiary hydroxyl groups were eliminated with $SOCl_2$-pyridine, the amorphous diene XIV hydrolysed with KOH and remethylated with CH_2N_2. The resulting unsaturated dihydroxy ester XV ($C_{21}H_{28}O_5$, m.p. 189-191°, $[\alpha]_D$

---

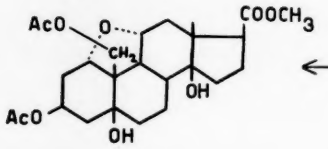
[4] H. Wieland, Ber.deutsch.chem.Ges. 45, 484, 2606 (1912); 46, 3327 (1913); 54, 2353 (1921); R.P.A. Sneeden and R.B. Turner, J.Amer.Chem.Soc. 77, 130, 190 (1955); A. Katz, Helv.Chim.Acta 40, 831 (1957); Ch. Tamm and A. Gubler, Helv.Chim.Acta 41, 297, 1762 (1958); 42, 239 (1959).

[5] Cf.p.ex.: F. Sondheimer, S. Burstein and R. Mechoulam, J.Amer.Chem.Soc. 82, 3209 (1960).

[6] K. Meyer and T. Reichstein, Helv.Chim.Acta 30, 1508 (1947).

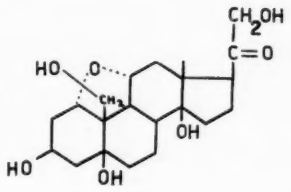
[7] M. Steiger and T. Reichstein, Helv.Chim.Acta 21, 828 (1938). F. Hunziker and T. Reichstein, Helv.Chim.Acta 28, 1472 (1945).

1960

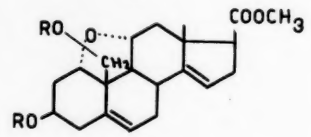


XII

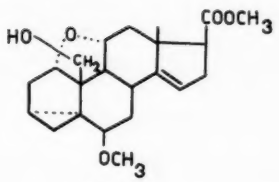
VI



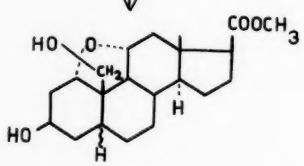
XIII



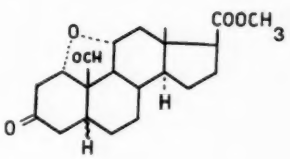
XIV (R = Ac) XV (R = H)



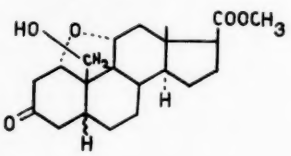
XVI



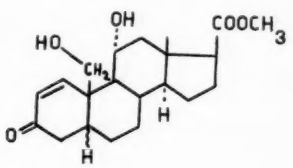
XVII



XVIII



XIX



XX

- 23° (chloroform)) gave with tetranitromethane a yellow colour and was transformed readily into the 3,5-cyclo-6β-methoxy derivative XVI ($C_{22}H_{30}O_5$, m.p. 139-142°, [α] - 37° (chloroform)) thus proving the 5-position of one double bond. Hydrogenation of XV with Pt in acetic acid gave the saturated dihydroxy ester XVII ($C_{21}H_{32}O_5$, m.p. 224-227°, $[\alpha]_D$ - 4° (chloroform)). By treatment of XVII with O_2-Pt^4 in aqueous acetone two products were formed, namely XVIII and XIX. Both of them proved to be unstable. The amorphous substance XVII gave on treatment with triethylamine the crystalline ester XX ($C_{21}H_{30}O_5$, m.p. 237-242°, λ_{max} 238 mμ, log ε 3.96 (ethanol)) characterized by a Δ^1-3-ketone group. The proof of structure of the keto aldehyde XVIII relies mainly on its spectroscopie properties. The I.R. spectrum showed no OH bands but peaks at 3.73 μ and at 5.81 - 5.85 μ with the former being assigned to the CH-streching frequency of the aldehyde group. The U.V. spectrum was characterized by a single maximum at 283-285 mμ, log ε 2.01 (ethanol) indicating two isolated carbonyl functions. The presence of the C-19 aldehyde was also shown by the n.m.r. spectrum having a typical peak at 868 c.p.s.

These findings eliminate the 1β,19-epoxide structure as the site of location for the oxygen bridge, and thus leave only the 1α,11α-epoxide ring for monoanhydro-ouabagenin (V) and its derivatives. The ready formation and the spatial arrangement of this ring can be interpreted as a transannular S_N2 type substitution of the axial 1β-hydroxyl group by the 11α-oxygen function. The sequence of reactions described opens a possibility for the synthesis of hormone analogues with an oxygen bridge and of 11-oxygenated $\Delta^{1,4}$-3-keto-steroids starting from ouabagenin.

All substances proved correct upon analysis. A detailed account of this work will be published in Helv.Chim.Acta.

1960